PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 413/14, 417/14, A61K 31/42, C07D 413/10 | A1

(11) International Publication Number: WO 99/28317

(43) International Publication Date: 10 June 1999 (10.06.99)

(21) International Application Number: PCT/GB98/03496

(22) International Filing Date: 24 November 1998 (24.11.98)

(30) Priority Data:
9725244.9 29 November 1997 (29.11.97) GB

(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

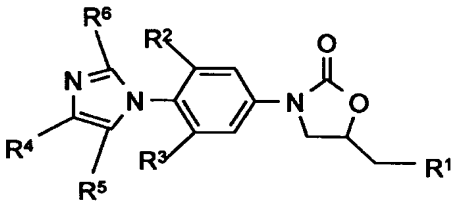
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BETTS, Michael, John [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). SWAIN, Michael, Lingard [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BRYANT, Tracey; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBSTITUTED PHENYLOXAZOLIDINONES AND THEIR USE AS ANTIBIOTICS



(I)

(57) Abstract

The invention concerns compounds of formula (I), wherein, for example, R^1 is of the formula $-NHC(=O)R^a$ wherein R^a is (1–4C)alkyl; R^2 and R^3 are independently hydrogen or fluoro; R^5 and R^6 are, for example, hydrogen; R^4 is –X–Y–Het.; wherein, for example, X is a direct bond and Y is $-(CH_2)_m-$ or $-CONH-(CH_2)_m-$; or X is $-(CH_2)_n-$ and Y is $-S(O)_p-(CH_2)_m-$; or X is $-CH_2O-$ or $-CH_2NH-$ and Y is $-CO-(CH_2)_m-$; wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and p is 0, 1 or 2; wherein Het. is a heterocyclic ring [unsaturated or saturated] optionally substituted by, for example, (1–4C)alkyl, halo, cyano, nitro or amino; pharmaceutically acceptable salts and *in vivo* hydrolysable ester thereof; processes for their preparation; pharmaceutical compositions containing them and their use as antibacterial agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SUBSTITUTED PHENYLOXAZOLIDINONES AND THEIR USE AS ANTIBIOTICS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing an oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

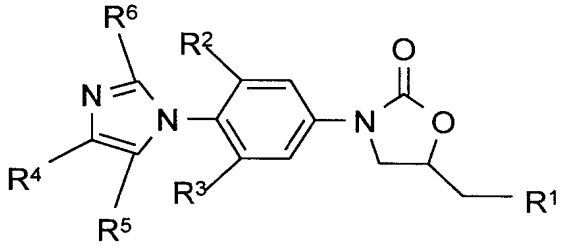
Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

The present inventors have discovered a class of antibiotic compounds containing an oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

We have now discovered a range of compounds which have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. In comparison with compounds described in the art (Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165) the compounds also possess a favourable toxicological profile.

Accordingly the present invention provides a compound of the formula (I):



(I)

wherein R^1 is hydroxy, amino, chloro, fluoro, (1-4C)alkanesulfonyloxy, azido, (1-4C)alkoxy, or of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

R^5 and R^6 are independently selected from hydrogen, (1-4C)alkyl, halo and trifluoromethyl;

R^4 is -X-Y-Het.;

wherein X is a direct bond or -CH(OH)- and

Y is $-(CH_2)_m-$, $-(CH_2)_n-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$ or $-C(=O)O-(CH_2)_m-$;

or wherein X is $-(CH_2)_n-$ or $-CH(Me)-(CH_2)_m-$ and

Y is $-(CH_2)_m-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$, $-C(=O)O-(CH_2)_m-$ or $-S(O)_p-(CH_2)_m-$;

or wherein X is $-CH_2O-$, $-CH_2NH-$ or $-CH_2N(R)-$ [wherein R is (1-4C)alkyl] and

Y is $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$ or $-C(=S)NH-(CH_2)_m-$; and additionally Y is $-SO_2-$ when X is $-CH_2NH-$ or $-CH_2N(R)-$ [wherein R (1-4C)alkyl], and Y is $-(CH_2)_m-$ when X is $-CH_2O-$ or $-CH_2N(R)-$;

wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and p is 0, 1 or 2; and when Y is $-(CH_2)_m-NH-(CH_2)_m-$ each m is independently selected from 0, 1, 2 or 3;

wherein Het. is a heterocyclic ring [which heterocyclic ring may be unsaturated (linked via either a ring carbon or ring nitrogen atom to -X-Y-) or saturated (linked via a ring nitrogen atom to -X-Y-), with the proviso that when it is unsaturated and linked via nitrogen to -X-Y- the ring is not quaternised] which heterocyclic ring is optionally substituted on an available carbon atom by up to three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkyl S(O)$_p$- (wherein p is 0, 1 or 2), carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, amino, N-(1-4C)alkylamino, di(N-(1-4C)alkyl)amino or (1-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkyl S(O)$_p$- (wherein p is 0, 1 or 2), carboxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, (2-4C)alkenyl, cyano, nitro, amino, (2-4C)alkanoylamino, (1-4C)alkoxy, di(N-(1-4C)alkyl)aminomethylimino, hydroxy, oxo or thioxo (=S); and optionally substituted on an available nitrogen atom (if the ring will not thereby be quaternised) by (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkyl S(O)$_p$- (wherein p is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di(N-(1-4C)alkyl)amino or (1-4C)alkanoylamino] or oxo (to form an N-oxide); and pharmaceutically acceptable salts thereof.

In a further aspect of the invention there is provided a compound of the formula (I) as described hereinabove, wherein when X is a direct bond, Y is additionally -CON(R)-$(CH_2)_m$- [wherein R is (1-4C)alkyl], and the optional substituents on an available carbon atom in the Het. heterocyclic ring additionally include imino.

The term 'alkyl' includes straight chained and branched structures. For example, (1-4C)alkyl includes propyl, isopropyl and t-butyl.

Examples of (1-4C)alkyl include methyl, ethyl, propyl, isopropyl and t-butyl; examples of N-(1-4C)alkylcarbamoyl include methylcarbamoyl and ethylcarbamoyl; examples of di(N-(1-4C)alkyl)carbamoyl include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of (1-4C)alkylS(O)$_p$- include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of (2-4C)alkenyl include allyl and vinyl; examples of (1-4C)alkoxy include methoxy, ethoxy and propoxy; examples of (2-4C)alkanoylamino include acetamido and propionylamino; examples of N-(1-4C)alkylamino include methylamino and ethylamino; example of di-(N-(1-4C)alkyl)amino

include di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino; examples of (1-4C)alkoxycarbonyl include methoxycarbonyl and ethoxycarbonyl; examples of halo include fluoro, chloro and bromo; examples of di-(N-(1-4C)alkyl)aminomethylimino include dimethylaminomethylimino and diethylaminomethylimino and examples of (1-4C)alkanesulfonyloxy include methylsulfonyloxy and ethylsulfonyloxy.

A heterocyclic ring means a 5- or 6-membered monocyclic ring or a 5/6 or 6/6 bicyclic ring (linked via either, or any, of the rings) containing up to four heteroatoms selected independently from O, S and N. An unsaturated ring means a fully unsaturated (aromatic) ring and partially unsaturated ring systems (such as, for example, tetrahydropyridine).

Preferred examples of unsaturated 5- or 6-membered heterocyclic groups with up to four heteroatoms selected independently from O, S and N are furan, pyrrole, thiophene, those containing one, two or three N atoms (for example, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- and 1,2,4-triazole), two N atoms and one S atom (for example 1,2,4- and 1,3,4-thiadiazole,), one N and one O atom (for example oxazole, isoxazole and oxazine) and one N and one S atom (for example thiazole and isothiazole). Unsaturated 5-membered heterocyclic groups are preferred. Thiazole is particularly preferred. Links via a ring carbon atom are preferred.

Preferred examples of a 5/6 or 6/6 bicyclic ring (linked via either of the rings) containing up to four heteroatoms selected independently from O, S and N are, for example, indole, quinoline, isoquinoline, benzpyrrole, benzpyrazole, benzimidazole, quinoxaline, benzthiazole, benzoxazole, benzthiadiazole, benztriazole and 1,4-benzodioxan. Preferred are 5/6 bicyclic rings, particularly those containing up to two heteroatoms only, such as benzthiazole and benzoxazole, especially benzthiazole. Links via a ring carbon atom are preferred.

It is to be understood that when a value for -X- is a two-atom link and is written, for example, as -CONH- it is the left hand part (-CO- here) which is bonded to the imidazole ring in formula (I) and the right hand part (-NH- here) which is bonded to -Y- in the definition of R^4. Similarly, when -Y- is a two-atom link and is written, for example, as -CONH- it is the left hand part of -Y- (-CO- here) which is bonded to the right hand part of -X-, and the right hand part of -Y- (-NH- here) which is bonded to the Het. moiety in the definition of R^4.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

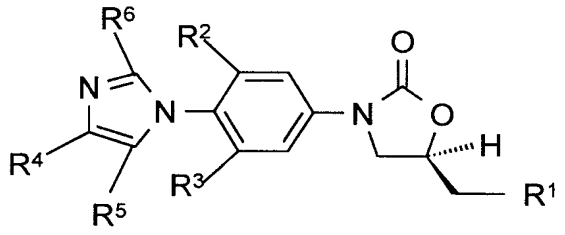
The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include in-vivo hydrolysable (in-vivo cleavable) esters of a compound of the formula (I).

An in-vivo hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and

N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

The compounds of the present invention have a chiral centre at the C-5 position. The pharmaceutically active enantiomer is of the formula (IA) :



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5(R) and 5(S) enantiomers, for example a racemic mixture. If a mixture of 5(R) and 5(S) is used, a larger amount (depending up on the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. Furthermore, some compounds of the formula (I) may have other chiral centres, for example when X is -CH(Me)-.

It will be appreciated that when the Het. moiety in R^4 is optionally substituted by hydroxy, oxo or thioxo the phenomenon of tautomerism may be present depending upon the nature of the Het. moiety. Thus, for example, in fully unsaturated (aromatic) systems a hydroxy substituent may represent one tautomeric form, and an oxo substituent the other tautomeric form. The invention includes all tautomeric forms which possess antibacterial activity.

Preferably R^1 is of the formula -NHC(=O)R^a wherein R^a is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl.

Yet more preferably R^1 is of the formula -NHC(=O)(1-4C)alkyl.

Most preferably R^1 is acetamido.

Preferably one of R^2 and R^3 is hydrogen and the other is fluoro.

Preferably R^5 and R^6 are hydrogen.

Preferably the Het. moiety in R^4 is unsaturated, ie. fully unsaturated (aromatic) ring or partially unsaturated ring systems. Preferably the Het. moiety in R^4 ring is linked via a ring carbon atom.

Preferred values for the Het. moiety in R^4 are furan, thiophene, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- and 1,2,4-triazole, 1,2,4- and 1,3,4-thiadiazole, oxazole, isoxazole, thiazole, isothiazole, indole, quinoline, isoquinoline, benzpyrazole, benzimidazole, quinoxaline, benzthiazole, benzoxazole, benzthiadiazole, benztriazole and 1,4-benzodioxan.

Preferred values for -X-Y- links are $-CH_2S-$, $-CH_2O-CO-$, $-CH_2NH-$, $-CH_2NHCO-$ and -CONH-.

Other preferred values for -X-Y- links are a direct link, $-CH_2SO_2-$, $-CH_2-$, $-CH_2NHSO_2-$, $-CH_2O-CO-CH_2-$, $-CO-O-CH_2-$, $-CO-O-CH_2-CH_2-$, $-CONH-CH_2-$, $-CONH-CH_2-CH_2-$, -CO- and -CON(Me)-.

Preferred optional substituents (preferably, zero, one or two) on an available carbon atom of the Het. moiety of R^4 are (1-4C)alkyl, halo, cyano, nitro, amino, (2-4C)alkanoylamino, (1-4C)alkoxy, hydroxy, oxo and thioxo (=S).

Preferred optional substituents (preferably, zero or one) on an available nitrogen atom of the Het. moiety of R^4 are (1-4C)alkyl, especially methyl, and oxo (to form an N-oxide).

Accordingly, in a particular aspect of the present invention there is provided a compound of the formula (I) in which R^1 is acetamido; one of R^2 and R^3 is hydrogen and the other is fluoro; R^5 and R^6 are hydrogen; the -X-Y- link is $-CH_2S-$, $-CH_2O-CO-$, $-CH_2NH-$, $-CH_2NHCO-$ or -CONH-; the Het. moiety in R^4 is a fully unsaturated (aromatic) ring linked via a ring carbon atom and selected from furan, thiophene, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- and 1,2,4-triazole, 1,2,4- and 1,3,4-thiadiazole, oxazole, isoxazole, thiazole, isothiazole, indole, quinoline, isoquinoline, benzpyrazole, benzimidazole, quinoxaline, benzthiazole, benzoxazole, benzthiadiazole, benztriazole and 1,4-benzodioxan; wherein the Het. moiety is optionally substituted by up to two substituents on an available carbon atom selected from (1-4C)alkyl, halo, cyano, nitro, amino, (2-4C)alkanoylamino, (1-4C)alkoxy, hydroxy, oxo and thioxo (=S), and optionally substituted by

a substituent on an available nitrogen atom selected from (1-4C)alkyl and oxo; and pharmaceutically-acceptable salts thereof.

Of the compounds in the above particular aspect, those in which the Het. moiety is a monocyclic ring are preferred.

An especially preferred compound of the invention is selected from the group consisting of :-

N-[(5S)-3-(3-Fluoro-4-(4-pyrimidin-2-ylthiomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-furoyloxymethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyridin-2-ylaminomethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(quinoxalin-2-ylcarbonylaminomethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

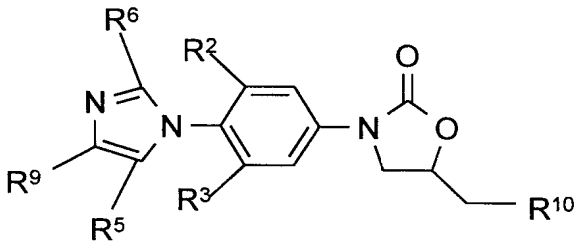
N-[(5S)-3-(3-Fluoro-4-(4-(thiazol-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and pharmaceutically-acceptable salts thereof.

Of the above, N-[(5S)-3-(3-Fluoro-4-(4-(thiazol-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide is especially preferred.

A further especially preferred compound of the invention is

N-[(5S)-3-(3-Fluoro-4-(thiazol-2-ylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and pharmaceutically-acceptable salts thereof.

In a further aspect the present invention provides a process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt thereof. The compounds of the formula (I) may be prepared by deprotecting a compound of the formula (II):



(II)

wherein R^2 , R^3, R^5 and R^6 are as hereinabove defined, R^9 is R^4 or protected R^4 and R^{10} is R^1 or protected R^1, and thereafter if necessary forming a pharmaceutically acceptable salt.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, t-butyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg t-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (eg trimethylsilyl,

t-butyldimethylsilyl, t-butyldiphenylsilyl); aryl lower alkyl groups (eg benzyl) groups; and triaryl lower alkyl groups (eg triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, eg p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (eg t-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (eg trimethylsilyl and t-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, metal- or enzymically-catalysed hydrolysis, for groups such as o-nitrobenzyloxycarbonyl, photolytically and for groups such as silyl groups, fluoride.

Examples of protecting groups for amide groups include aralkoxymethyl (eg. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (eg. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (eg. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (eg. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (eg. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (eg. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (eg. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (eg. 2,4-di(methoxy)benzyl); and alk-1-enyl (eg. allyl, but-1-enyl and substituted vinyl eg. 2-phenylvinyl).

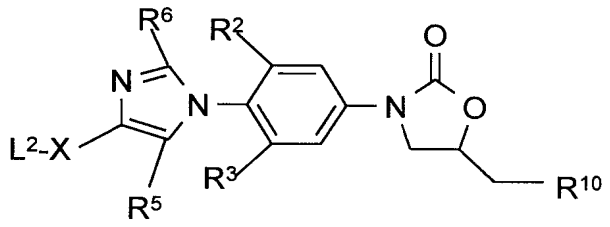
Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid, or in the case of the silyl containing groups fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

For further examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons).

In another aspect of the present invention the compounds of the formulae (I) and (II) and pharmaceutically acceptable salts thereof can be prepared:

(a) by modifying a substituent in or introducing a substituent into another compound of the formula (I) or (II), or modifying a linking group in another compound of the formula (I) or (II);

(b) by reaction of a compound of the formula (III) with a compound of the formula Het-Y-L^1 [wherein L^1 and L^2 are independently hydrogen or a leaving group], or with a compound capable of forming a Het. moiety [wherein L^2 may form part of the final Het. moiety], or with a Het-Y-L^1 compound such that -Y-L^1 or L^2-X- (or a part thereof) may form part of the final -X-Y- link;

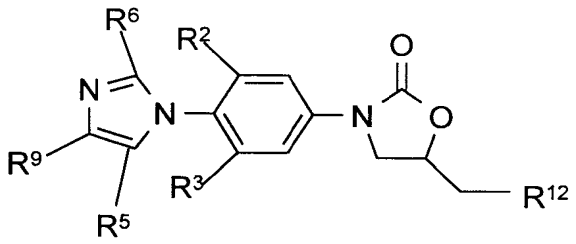


(III)

(c) when R^1 or R^{10} is of the formula -NHC(=O)R^a, by introducing -C(=O)R^a into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

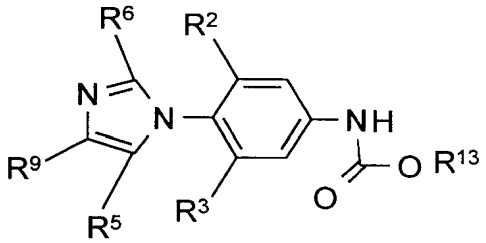
(d) when R^1 or R^{10} is amino, by reducing a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

(e) when R^1 or R^{10} is azido, by reacting a compound of the formula (IV) [wherein R^{12} is mesyloxy, tosyloxy or a phosphate ester] with a source of azide:

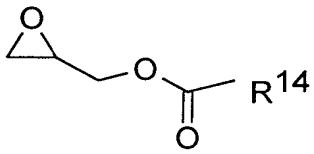


(IV)

(f) when R^1 or R^{10} is hydroxy, by reacting a compound of the formula (V) with a compound of the formula (VI) [wherein R^{13} is (1-6C)alkyl or benzyl, and R^{14} is (1-6C)alkyl]:



(V)



(VI)

(g) when R^{10} is of the formula $-N(CO_2R^{15})CO(1\text{-}4C)alkyl$ [wherein R^{15} is (1-4C)alkyl or benzyl], from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(h) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(i) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (IV);

wherein L^2, L^1, X, Y, R^2, R^3 , R^5 , R^6 and R^9 are as hereinabove or hereinafter defined, and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically acceptable salt;

iii) forming a suitable N-oxide.

The processes (a) and (c) to (i) may be performed using compounds of the formula (I) or (II) as defined hereinbefore with compounds of the formula (II) in which R^9 is -X-L^2 (or a protected version thereof - see hereinbefore and Examples for suitable protecting groups). The process (b) may then be performed using the compound in which -X-L^2 is unprotected. Certain values of assembled -X-Y- links in compounds of formula (I) and (II) (wherein R^9 is R^4 or protected R^4) are unsuitable for use with processes (a) and (c) to (i); the skilled organic chemist will recognise when this is so, and, for example, the oxazolidinone ring should be assembled before the -X-Y- link is assembled.

Certain intermediate compounds described hereinbefore and hereinafter, for example those in which -X-L^2 in a compound of formula (II) is azidomethyl are novel and are provided as a further feature of the invention.

Process (a)

Methods for converting substituents into other substituents are known in the art. For example a cyano group reduced to an amino group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, a bromo group to a cyano group, a thio group oxidised to a sulfinyl or sulfonyl group, a (1-4C)alkoxycarbonyl group converted to a carbamoyl group (see Example 27, for example) or an amino group converted to a (2-4C)alkanoylamino group (see Example 48, for example).

A linking group in one compound of the formula (I) or (II) may be converted into another linking group, for example, a -CO- link may be converted into a -CH(OH) link.

Process (b)

It will be appreciated that process (b) provides means for assembling the -X-Y- link in compounds of the formula (I). In describing the reactions suitable for this assembly the terms L^2-X- and -Y-L^1 have been used to define certain intermediate compounds, but the terms L^2, X, Y and L^1 are not necessarily strictly limited to those defined hereinbefore. Thus, for example, amide links may be established by reaction of a compound of formula (III) in

which L^2-X- is a carboxy group (i.e. L^2 is -OH and X is -CO-) with a Het.-Y-L^1 compound wherein Y is -NH- and L^1 is H. The -X-Y- link in this case (-CONH-) is provided for in the definition of compounds of formula (I) hereinbefore by X as a direct bond and Y as -CONH-$(CH_2)_m$- with m is 0. Thus, process (b) includes those processes in which compounds of formula (III) and Het.-Y-L^1 are such that L^2-X- and -Y-L^1 (or a part thereof) are suitable to give an assembled -X-Y- link as defined hereinbefore. The skilled organic chemist will recognise from the range of assembled -X-Y- links and the description for process (b) given hereinbefore and hereinafter how such -X-Y- links may be assembled.

The coupling reaction between a compound of the formula (III) and a compound of the formula Het-Y-L^1 is conveniently performed in an inert solvent such as acetonitrile, dichloromethane, N,N-dimethylformamide or N,N-dimethylacetamide, at a temperature in the range 0°C to the reflux temperature of the solvent, preferably in the range ambient to 70°C. The precise reaction conditions and the nature of the starting materials will depend upon the nature of the -X-Y- bond that is to be formed between the imidazole ring in the compound of formula (III) and the Het. group in R^4 or R^9. The skilled organic chemist will be able to select suitable starting materials and conditions to produce the range of -X-Y- bonds detailed in this specification, and non-limiting representative examples are provided in the Examples contained herein. Suitable values for the leaving groups L^1 and L^2 are provided below. For example:-

Methylthio linkages (X is -CH_2-, Y is -S-) may be prepared by the reaction of an (activated) methylhydroxy compound (X is -CH_2-, L^2 is -OH or another suitable leaving group prepared from -OH) with a thioxo or thiol compound (-Y-L^1 is =S, or Y is -S- and L^1 is -H) in the presence of an agent such as N,N-dimethylformamide dineopentylacetal (DMFDMPA) which activates the -OH group for displacement and also generates an in-situ base for generating the required nucleophile.

Methylamino linkages (X is -CH_2NH-, Y is a direct bond) may be prepared by the reaction of a methylamino compound (X is -CH_2NH-, L^2 is -H) with, for example, a halo compound (-Y-L^1 is -halo, Y is a direct bond, L^1 is halo).

Amide (for example methylaminocarbonyl) linkages (X is -CH_2NH-, Y is -CO-) may be prepared by the reaction of a methylamino compound (X is -CH_2NH-, L^2 is -H) with an acid chloride compound (-Y-L^1 is -COCl, Y is -CO-, L^1 is chloro). Other amide linkages (for

example carbonylamino(1-4C)alkyl and carbonylamino; X is -CONH-, Y is -$(CH_2)_n$- wherein n is 0, 1, 2 or 3) may be prepared by the reaction of an activated carboxy compound (X- L^2 is -CO_2H, L^2 is -OH) with an amine (-Y-L^1 is -$(CH_2)_nNH_2$, L^1 is -H), optionally in the presence of a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide. Suitable activated carboxy compounds are, for example, the esters formed from the reaction of the carboxy compound with 4-nitrophenol, or 1-hydroxybenzotriazole.

Amide linkages in which the nitrogen atom of the amide bond is provided by a ring nitrogen atom in a non-aromatic Het. moiety can be prepared from a carboxy compound (X is -CO-, Y is -$(CH_2)_n$- wherein n is 0, ie. a direct bond) may be prepared by the reaction of an activated carboxy compound (X-L^2 is -CO_2H, L^2 is -OH) with a non-aromatic nitrogen containing Het. compound (optionally with functionalities protected, -Y- is a direct bond, -L^1 is -H), optionally in the presence of a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide.

Amide (urea or thiourea) linkages in which -Y-L^1 or L^2-X- may form part of the final -X-Y- link may be prepared from the reaction of a compound of the formula (III) in which L^2-X- is an isocyanate or isothiocyanate group with a Het.-$(CH_2)_m$-amine (wherein m is 0 to 3). Alternatively, Het.-$(CH_2)_m$-NCO or Het.-$(CH_2)_m$-NCS may be reacted with a compound of the formula (III) in which L^2-X- is an amine group (wherein m is 0 to 3). These reactions illustrate cases in which -Y-L^1 or L^2-X- is -$(CH_2)_m$-amine, or-$(CH_2)_m$-NCO or -$(CH_2)_m$-NCS.

Similarly, sulfonamide (for example methylaminosulfonyl) linkages (X is -CH_2NH-, Y is -SO_2-) may be prepared by the reaction of a methylamino compound (X is -CH_2NH-, L^2 is -H) with a sulfonyl chloride compound (-Y-L^1 is -SO_2Cl, Y is -SO_2-, L^1 is chloro).

Ester linkages (for example methoxycarbonyl) linkages (X is -CH_2O-, Y is -CO-) may be prepared by the reaction of a methylhydroxy compound (X is -CH_2O-, L^2 is -H) with carboxy compound (-Y-L^1 is -CO_2H, L^1 is -OH) in the presence of a coupling agent such as DMFDMPA which activates the -OH group for displacement and also generates an in-situ base for generating the required nucleophile. Other ester linkages (for example carbonyloxymethyl; X is a direct bond, Y is -C(=O)O-CH_2-) may be prepared by the reaction of a carboxy compound (X-L^2 is -CO_2H-, L^2 is -OH) with a methylhydroxy compound (-Y-L^1 is -CH_2OH, L^1 is -H) in the presence of a coupling agent such as dimethylaminopyridine and dicyclohexylcarbodiimide.

Alkylene chain linkages (for example X is methylene, $-CH_2-$) to a ring nitrogen atom in a non-aromatic Het. moiety can be prepared, for example, by reaction of a methylhydroxy compound (X is $-CH_2-$, L^2 is -OH) with a non-aromatic Het. compound (optionally with functionalities protected, -Y- is a direct bond, $-L^1$ is -H), optionally in the presence of a coupling agent such as N,N-dimethylformamide dineopentylacetal (DMFDMPA) which activates the -OH group for displacement and also generates an in-situ base for generating the required nucleophile.

Direct bond linkages (in which the Het. moiety of R^4 is linked directly to the imidazole ring in the compound of formula (III)) may be formed, for example by reaction of a compound of formula (III) in which L^2-X- is formyl (L^2 is =O here) with a compound capable of forming a Het. moiety incorporating the formyl carbon atom as part of the Het. ring. Thus, as illustrated in Examples 81 and 82, a diamine (such as 2-aminoaniline) may be reacted with the formyl compound (to give a benzimidazole moiety as Het., directly C-linked to the imidazole ring of the product compound).

The reaction between a compound of the formula (III) and a compound capable of forming a Het. moiety may be performed, for example, using a compound of the formula (III) in which L^2-X- is azidomethyl to form a 1,2,3-triazole ring upon reaction with ethyl propiolate. In this case L^2 is not a leaving group as all three nitrogen atoms of the azido group are incorporated in the 1,2,3-triazole ring.

Compounds of the formula (III) may be prepared by using the processes described in this specification, and as, for example, illustrated in the accompanying Examples. Thus, for example, a compound of the formula (III) in which L^2-X- is hydroxymethyl may be prepared using process (f), ie. from a compound of the formula (V) in which R^9 is hydroxymethyl (or protected hydroxymethyl). This hydroxymethyl group may be modified to a azidomethyl group, which may then be reduced to an aminomethyl group (see, for example, Example 19 preparation of intermediate). Such modifications are known in the art. The hydroxymethyl group may also be oxidised to an alkanoyl (eg. formyl) group, and further oxidised to a carboxy group, using known oxidising techniques and reagents.

The preparation of compounds of the formula Het.-Y-L^1 , Het.-$(CH_2)_m$-amine, Het.-$(CH_2)_m$-NCO or Het.-$(CH_2)_m$-NCS (wherein m is 0 to 3) and of compounds capable of forming a Het. moiety, is within the skill of the skilled organic chemist, or are commercially available.

Process (c)

When R^a is (1-4C)alkyl, the group -C(=O)(1-4C)alkyl may be introduced into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino by standard acetylation procedures. For example, the amino group may be acetylated to give an acetamido group using the Schotten-Baumann procedure i.e. reacting the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino with acetic anhydride in aqueous sodium hydroxide and THF in a temperature range of 0°C to 60°C , preferably between 0°C and ambient temperature. The acylation may be carried out in situ following the catalytic hydrogenation of a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido, by performing the hydrogenation in the presence of acetic anhydride (for example using similar methods to those used in example 4).

When R^a is hydrogen, the -CHO group may be introduced into the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino (amino compound) by reacting the latter compound in formic acetic anhydride, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature, or by reacting it with ethyl formate in an inert organic solvent in the temperature range of 50-100°C.

When R^a is (1-4C)alkoxy, the -COO(1-4C)alkyl group may be introduced into the amino compound by reacting the latter compound with (1-4C)alkyl chloroformate, in the presence of an organic base such as triethylamine, in an organic solvent such as dichloromethane and in a temperature range of 0°C to ambient temperature.

When R^a is chloromethyl, dichloromethyl, cyanomethyl or methoxymethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with the appropriate acid chloride under standard conditions. The acid chloride may be prepared from the appropriate acid. When R^a is acetylmethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with diketene, in an inert organic solvent such as THF, in a temperature range of 0^oC to ambient temperature.

Alternatively, the amino compound may be reacted with the appropriate acid anhydride, in dichloromethane or THF, in the presence of an organic base such as triethylamine and in a temperature range of 0°C to ambient temperature, or the amino

compound may be reacted with the appropriate acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an organic base such as triethylamine, in an organic solvent such as dichloromethane, in a temperature range of 0°C to ambient temperature.

Process (d)

Suitable reducing agents for reducing azido to amino in a compound of the formula (I) or (II) include triethylamine/hydrogen sulfide, triphenylphosphine or phosphite ester, or hydrogen in the presence of a catalyst. More specifically the reduction of the azido group may be carried out by heating it in an aprotic solvent, such as 1,2-dimethoxyethane, in the presence of $P(OMe)_3$ and subsequently heating in 6N aqueous hydrochloric acid, or reacting it with hydrogen in the presence of palladium on carbon in a protic such as DMF or ethyl acetate. For further details on the reduction of azides to amines see USP 4,705,799. The azido compound may be reduced and converted to a compound of the formula (I) or (II), wherein R^1 or R^{10} is acetamido, in situ using acetic anhydride in DMF.

Process (e)

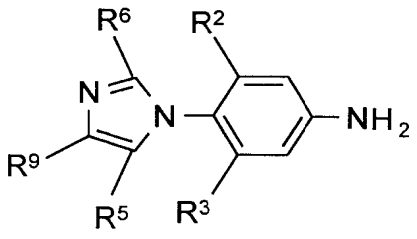
A compound of the formula (I) or (II) wherein R^1 or R^{10} is azido may be prepared, for example, by reacting a compound of the formula (IV) with sodium azide in an inert solvent such as DMF in a temperature range of ambient to 100°C, normally in the region of 75°C - 85°C. A compound of the formula (IV) may be prepared by converting the hydroxy group in a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy into a tosyloxy or mesyloxy group by standard methods known in the art. For example, by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy with tosyl chloride, mesyl chloride or a chlorophosphate ester in the presence of a mild base such as triethylamine, or pyridine.

Process (f)

Compounds of the formulae (V) and (VI) are conveniently reacted together in the presence of a strong base such as butyl lithium, lithium bistrimethylsilylamide, sodium hydride, or lithium diisopropylamide. The reaction is conveniently carried out in an inert solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), N,N^1-dimethylpropyleneurea (DMPU) or N-methylpyrrolidone in a temperature range of -78°C to -

50°C for the deprotonation and cyclisation. Suitable values for R^{13} include ethyl and benzyl and suitable values for R^{14} include ethyl and n-propyl, preferably n-propyl.

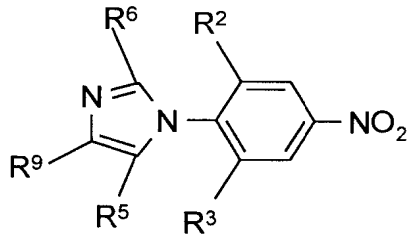
A compound of the formula (V) is conveniently prepared by reacting a chloroformate of the formula ($ClCOOR^{13}$) with a compound of the formula (VA):



(VA)

wherein R^2, R^3, R^5, R^6 and R^9 are as hereinabove defined. The reaction is conveniently carried out in the presence of an inorganic or organic base such as sodium bicarbonate or an amine base such as dimethylaniline, the former in a solvent such as acetone/water and the latter in an organic solvent such as THF, toluene, DMF or acetonitrile.

A compound of the formula (VA) may be prepared by reducing a compound of the formula (VB):

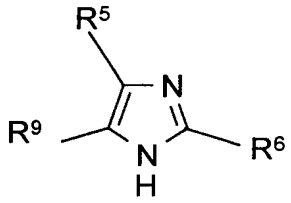


(VB)

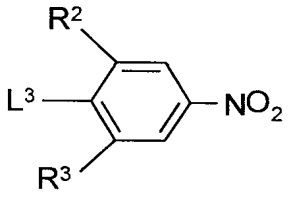
wherein R^2, R^3, R^5, R^6 and R^9 are as hereinabove defined.

Many reduction methods suitable for the reduction of a nitro to an amino group are known in the art, for example catalytic hydrogenation, metal reductions or with reducing agents such as sodium hydrosulfite. Suitable catalysts in catalytic hydrogenation include Raney nickel, platinum metal and its oxide, rhodium, palladium-on-charcoal and Wilkinson's catalyst RhCl ($Ph_3P)_3$. Catalyst hydrogenation is conveniently carried out in the temperature range 0°C - 150°C, but preferably at ambient temperature at slightly above atmospheric pressure.

A compound of the formula (VB) is conveniently prepared by reacting together compounds of the formulae (VC) and (VD):



(VC)



(VD)

wherein R^2, R^3, R^5, R^6 and R^9 are as hereinabove defined and L^3 is a leaving group, preferably halo and in particular fluoro.

The reaction between compounds of the formulae (VC) and (VD) is carried out in the presence of an organic or inorganic base such as sodium bicarbonate, potassium carbonate or an amine base such as diisopropylethylamine, in an inert solvent such as acetonitrile, DMF, DMPU or N-methylpyrrolidone, in a temperature range of 50°C - 150°C.

Compounds of the formula (VC) may be prepared by introducing substituents into or modifying substituents in a known optionally substituted imidazole ring. Such conversions are well known to the skilled chemist, for example a cyano group may be hydrolysed to a carboxy group which in turn may be converted to a carbamoyl or alkoxycarbonyl group or reduced to a hydroxymethyl group; an amino group may be acylated to an alkanoylamino group; a thio group may be alkylated to an alkylthio group which in turn may be oxidised to an alkylsulfinyl or alkylsulfonyl group and a hydroxyalkyl group may be alkylated to an alkoxyalkyl group.

Alternatively compounds of the formula (VC) may be prepared using the methods described in Houben-Weyl, Methoden der organischen Chemie, Heterarene III Teil 3, ed E Schaumann (1994), or The Chemistry of Heterocyclic Compounds, Vol 6, Part 1 "Imidazole and its Derivatives" (1953).

Process (g)

A compound of the formula (II) wherein R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl is conveniently prepared by reacting a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy with an amide of the formula

$HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ under Mitsunobu conditions. For example, in the presence of tri-n-butylphosphine and 1,1'-(azodicarbonyl)dipiperidine in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of analogous Mitsunobu reactions are contained in Tsunoda et al, Tet. Letts., 34, 1639, (1993).

Amides of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ may be prepared by standard procedures of organic chemistry which are within the ordinary skill of an organic chemist.

Process (h)

A compound of the formula (I) or (II) wherein R^1 or R^{10} is fluoro may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When R^1 or R^{10} is chloro, the compound of the formula (I) or (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with sulfinyl chloride in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature.

The (1-4C)alkanesulfonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride in the presence of a mild base such as triethylamine or pyridine.

The (1-4C)alkylaminocarbonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkyl cyanate in an organic solvent such as THF or acetonitrile, in the presence of triethylamine, in a temperature range of 0°C to 50°C.

Process (i)

A compound of the formula (I) or (II) wherein R^1 or R^{10} is chloro may also be prepared from a compound of the formula (IV), by reacting the latter compound with lithium chloride and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux. A compound of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylthio or (1-4C)alkoxy may be prepared by reacting the compound of the formula

(IV) with sodium thio(1-4C)alkoxide or sodium (1-4C)alkoxide respectively, in an alcohol or THF, in a temperature range of 0°C to reflux.

Suitable N-oxides of compounds of the formula (I) or (II) may be prepared directly from a corresponding parent compound of the formula (I) or (II) using techniques well known to the ordinary skilled organic chemist, such as, for example, using a peracid (such as m-chloroperbenzoic acid) or perphthalic acid in a suitable solvent (such as dioxan or a mixture of water and THF) at a suitable temperature (such as ambient temperature). The preparation of suitable N-oxides by assembly from suitable N-oxide starting materials and the use of the processes described in this specification is within the skill of the ordinary skilled organic chemist, and is illustrated by, for example, Example 5.

When an optically active form of a compound of the formula (I) is required, it may be obtained, by carrying out one of the above procedures using an optically active starting material or by resolution of a racemic form of the compound or intermediate using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

The invention also provides the use of a compound of the present invention, or a pharmaceutically-acceptable salt thereof, for use as a medicament; and the use of a compound of the present invention, or a pharmaceutically-acceptable salt thereof, in the manufacture of a novel medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt thereof and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents (for example ß-lactams or aminoglycosides). These may include penicillins, for example oxacillin or flucloxacillin, carbapenems (for example meropenem or imipenem) and monobactams (for example aztreonam) to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein product (BPI) or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100mg and 1g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Antibacterial Activity

The pharmaceutically acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S. aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The antibacterial properties of the compounds of the invention may also be demonstrated in vivo in conventional tests.

The following results were obtained on a standard in vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot.

The organisms were tested on a standard semi-defined susceptability test medium (IsoSensitest agar), using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours.

Organism		MIC (µg/ml)
		Example 43
Staphylococcus aureus:		
	Oxford	0.125
	Novb. Res	0.25
	MRQR	1.0
Coagulase Negative Staphylococcus		
	MS	0.06
	MR	0.25
Streptococcus pyogenes		
	C203	0.125
Enterococcus faecalis		0.5
Bacillus subtilis		0.25

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

The invention is now illustrated by the following Examples in which unless otherwise stated:-

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-26° (temperatures are in degrees Celsius ^{o}C) and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end-products of the formula I were confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard

(δ scale) and peak multiplicities are shown thus: br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet, m, multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected];

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis;

(vii) in which the following abbreviations may be used :-

MPLC	is medium pressure chromatography
TLC	is thin layer chromatography
DMSO	is dimethylsulfoxide
$CDCl_3$	is deuterated chloroform
MS	is mass spectroscopy
ESP	is electrospray
CI	is chemical ionization
DMF	is N,N-dimethylformamide
THF	is tetrahydrofuran

and

(viii) when product acetamide structures are shown the pharmaceutically-active enantiomer ((5S)-methylacetamide) is shown.

Example 1: N-[(5S)-3-(3-Fluoro-4-(4-pyrimidin-2-ylthiomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (174 mg, 0.5 mM) and pyrimidine-2-thione (112 mg, 1 mM) were suspended in dry acetonitrile (20 ml), and *N,N*-dimethylformamide dineopentyl acetal (462 mg, 2 mM) added. The mixture was heated to reflux for 6 hours giving a solution. Solvent was evaporated, the residue dissolved in dichloromethane, and subjected to mplc on silica, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (204 mg) as a gum.

MS (ESP): 443 (MH^+) for $C_{20}H_{19}FN_6O_3S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.41 (t, 2H); 3.75 (dd, 1H); 4.13 (t, 1H); 4.34 (s, 2H); 4.74 (m, 1H); 7.21 (t, 1H); 7.41 (dd, 1H); 7.46 (s, 1H); 7.63 (t, 1H); 7.71 (dd, 1H); 7.94 (t, 1H); 8.23 (brt, 1H); 8.64 (d, 2H).

The intermediate for this compound was prepared as follows :-

3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)nitrobenzene

3,4-Difluoronitrobenzene (23.85 g) was dissolved in acetonitrile (180 ml), followed by 4-hydroxymethylimidazole (14.7 g) and ethyldiisopropylamine (65.2 ml). The mixture was stirred and heated to reflux for 2 days. After cooling, acetonitrile was evaporated and the residue was shaken with a mixture of methyl *t*-butyl ether (200 ml) and water (100 ml), and the solid filtered. After washing with a mixture of methyl *t*-butyl ether (50 ml) and water (25 ml), the solid was dried *in vacuo* at 60°C overnight, to give product (26.8 g) mp 157-159°C.

MS (CI): 238 (MH^+) for $C_{10}H_8FN_3O_3$

NMR (DMSO-D6) δ: 4.57 (d, 2H); 5.18 (t, 1H); 7.66 (t, 1H); 8.11 (t, 1H); 8.28 (t, 1H); 8.35 (dm, 1H); 8.54 (dd, 1H).

3-Fluoro-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)nitrobenzene

3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)nitrobenzene (26.7 g) and imidazole (15.3 g) were suspended in dry *N,N*-dimethylformamide (190 ml) and stirred under argon on an ice-bath. *t*-Butyldimethylsilylchloride (25.5 g) was added in one portion, and stirring continued at ice temperature for 30 minutes, then at ambient temperature overnight. Solvent was evaporated

in vacuo at 30°C, the residue diluted with water (200 ml) and extracted into ethyl acetate (700 ml). After washing with water (2 x 300 ml), brine, and drying over magnesium sulfate, solvent was evaporated (finally on high vacuum) to give an oil which solidified (39.2 g). This was used in the next stage with no further purification.

NMR (DMSO-D6) δ: 0.00 (s, 6H); 0.82 (s, 9H); 4.55 (s, 2H); 7.44 (m, 1H); 7.89 (t, 1H); 8.06 (t, 1H); 8.14 (dm, 1H); 8.33 (dd, 1H).

1-Amino-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)fluorobenzene

3-Fluoro-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)nitrobenzene (39.0 g) was dissolved in a mixture of methanol (220 ml) and tetrahydrofuran (890 ml) and stirred under argon in an ice-bath. Ammonium formate (35.2 g) was added, followed by 10% palladium on charcoal (1.6 g), and the mixture allowed to warm to ambient temperature. Stirring was continued for 2 days. TLC showed a trace of remaining starting material, so further palladium catalyst (0.5 g) was added, and more ammonium formate (35 g) in portions over 6 hours, before leaving to stir overnight, giving essentially one spot as product. The catalyst was filtered off on celite, the cake washed well with methanol/tetrahydrofuran, and filtrates evaporated to dryness. The residue was partitioned between ethyl acetate (700 ml) and water (200 ml), the organic layers washed with water, brine, and dried over magnesium sulfate. Evaporation gave an oil (36 g), used in the next stage with no further purification.

MS (ES): 322 (MH^+) for $C_{16}H_{24}FN_3OSi$

NMR (DMSO-D6) δ: 0.04 (s, 6H); 0.85 (s, 9H); 4.56 (s, 2H); 5.63 (s, 2H); 6.45 (dd, 1H); 6.48 (dd, 1H); 7.12 (t, 1H); 7.13 (s, 1H); 7.69 (s, 1H).

1-Benzyloxycarbonylamino-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)fluorobenzene

1-Amino-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)fluorobenzene (36.1 g) was dissolved in dry dichloromethane (450 ml), treated with pyridine (11.3 ml), then stirred under argon while cooling to -20°C. Benzyl chloroformate (17.7 ml) in dichloromethane (50 ml) was added dropwise, maintaining the temperature. The mixture was then allowed to warm to ambient temperature over 1 hour, then stirred for a further 1.5 hours. The mixture was diluted with aqueous sodium bicarbonate (250 ml), and the organic layer separated. A further extraction with dichloromethane (200 ml) was made, the combined organic layers dried over

magnesium sulfate, and solvent evaporated. The resulting oil was re-evaporated with toluene, and purified by chromatography on silica (500 g) in a sinter column, eluting with a gradient from CH_2Cl_2 to 50% EtOAc in CH_2Cl_2. Evaporation, then re-evaporation with toluene gave solid product (51 g).

MS (ES): 456 (MH^+) for $C_{24}H_{30}FN_3O_3Si$

NMR (DMSO-D6) δ: 0.00 (s, 6H); 0.77 (s, 9H); 4.53 (s, 2H); 5.11 (s, 2H); 7.24-7.40 (complex, 7H); 7.46 (t, 1H); 7.53 (dd, 1H); 7.79 (s, 1H); 10.10 (s, 1H).

(5R)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-5-hydroxy-methyloxazolidin-2-one

t-Butanol (6.1 g) in dry tetrahydrofuran (50 ml) was stirred under argon at -10°. *n*-Butyllithium in *iso*hexane (1.6M, 41.3 ml) was added dropwise, the mixture stirred for 10 minutes, then cooled to -70° . A solution of 1-benzyloxycarbonylamino-4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)fluorobenzene (25.0 g) in dry tetrahydrofuran (150 ml) was added dropwise over 20 minutes, then stirred for 20 minutes at -70°C . (*R*)-glycidylbutyrate (9.5 g) in tetrahydrofuran (10 ml) was added dropwise over 10 minutes, keeping the temperature below -60°C. Stirring was continued overnight, allowing the temperature to rise to ambient. Saturated sodium bicarbonate solution (200 ml) was added, and the mixture extracted with ethyl acetate (500 and 200 ml). After drying over magnesium sulfate and evaporation the residue was purified by chromatography on silica, eluting with a gradient from dichloromethane to 20% MeOH in dichloromethane. Relevant fractions were combined and evaporated to give a gum (20.5 g).

MS (ES): 422 (MH^+) for $C_{20}H_{28}FN_3O_4Si$

NMR (DMSO-D6) δ: 0.02 (s, 6H); 0.81 (s, 9H); 3.49 (brd, 1H); 3.63 (brd, 1H); 3.80 (dd, 1H); 4.06 (t, 1H); 4.55 (s, 2H); 4.68 (s, 1H); 5.14 (brs, 1H); 7.30 (s, 1H); 7.41 (dm, 1H); 7.58 (t, 1H); 7.68 (dd, 1H); 7.85 (t, 1H).

(5R)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-5-methanesulfonyloxymethyloxazolidin-2-one

(5R)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluoro-phenyl)-5-hydroxymethyloxazolidin-2-one (8.0 g) was dissolved in dry dichloromethane (60ml) with stirring under argon in an ice-bath. Triethylamine (3.44 ml) was added, followed by dropwise addition of methanesulfonyl chloride (1.62 ml). Stirring was continued for 2 hours as the mixture warmed to ambient temperature. Aqueous sodium bicarbonate was added, the organic layer separated, and further extracted with dichloromethane. Combined extracts were dried over magnesium sulfate. Evaporation gave a gum (9.4 g), which was dried under high vacuum, and used as such in the next stage.

NMR (DMSO-D6) δ: 0.07 (s, 6H); 0.88 (s, 9H); 3.46 (s, 3H); 3.88 (dd, 1H); 4.25 (t, 1H); 4.49 (m, 2H); 4.61 (s, 2H); 5.06 (m, 1H); 7.36 (s, 1H); 7.46 (dm, 1H); 7.67 (t, 1H); 7.84 (dd, 1H); 7.94 (t, 1H).

(5R)-5-Azidomethyl-3-(4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-oxazolidin-2-one

(5R)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-5-methanesulfonyloxymethyloxazolidin-2-one (13.6 g) was dissolved in dry *N*,*N*-dimethylformamide (110 ml). Sodium azide (3.53 g) was added, and the mixture was heated at 80°C for 3.5 hours. The mixture was cooled, diluted with water (1.1 L) containing sodium bicarbonate (2 g), and extracted with ethyl acetate (2 x 800 ml). Combined organics were washed with water (2 x 300 ml), then brine, and dried over magnesium sulfate. The solution was evaporated to a small volume (~100 ml), and insolubles filtered. The ethyl acetate soluble material was columned on silica (100 g), eluting with ethyl acetate. Product fractions were combined and evaporated to give a gum (10.0 g).

MS (ES): 447 (MH^+) for $C_{20}H_{27}FN_6O_3Si$

NMR (DMSO-D6) δ: 0.08 (s, 6H); 0.87 (s, 9H); 3.71 (dd, 1H); 3.79 (dd, 1H); 3.84 (dd, 1H); 4.20 (t, 1H); 4.61 (s, 2H); 4.93 (m, 1H); 7.36 (s, 1H); 7.46 (dm, 1H); 7.65 (t, 1H); 7.75 (dd, 1H); 7.93 (t, 1H).

N-[(5S)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

To (5R)-5-azidomethyl-3-(4-(4-*t*-butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-oxazolidin-2-one(10.0 g) in ethyl acetate (560 ml) was added triethylamine (13.3 ml), acetic anhydride (4.5 ml), and palladium catalyst (10% on charcoal, 1.5 g), and the mixture hydrogenated at ambient temperature for 17 hours. The mixture was filtered through celite, the celite washed well with ethyl acetate, and the organic layer stirred with a saturated solution of sodium bicarbonate (100 ml) at ambient temperature for 1 hour. The organic layer was separated, dried over magnesium sulfate, and evaporated. Crude product (15 g, from two batches) was dissolved in dichloromethane and chromatographed on silica, eluting with a gradient from dichloromethane (100%) to 10% methanol in dichloromethane. Product fractions were combined to give a gum (12.3 g).

MS (ES): 463 (MH^+) for $C_{22}H_{31}FN_4O_4Si$

NMR (DMSO-D6) δ: 0.00 (s, 6H); 0.81 (s, 9H); 1.77 (s, 3H); 3.36 (t, 2H); 3.71 (dd, 1H); 4.08 (t, 1H); 4.54 (s, 2H); 4.77 (m, 1H); 7.29 (s, 1H); 7.38 (dm, 1H); 7.59 (t, 1H); 7.64 (dd, 1H); 7.87 (t, 1H); 8.18 (brt, 1H).

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide

N-[(5S)-3-(4-(4-*t*-Butyldimethylsilyloxymethylimidazol-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (6.0 g) was dissolved in a mixture of acetic acid (60 ml), tetrahydrofuran (20 ml) and water (20 ml), and left to stir overnight at ambient temperature. Solvents were evporated at 40° *in vacuo* to give a gum. This was dissolved in dichloromethane (25 ml), and dry diethyl ether (100 ml) stirred in. The precipitate was triturated and stirred until properly solid, then filtered, washed with ether, and dried *in vacuo* to give product (3.7 g).

MS (ES): 349 (MH^+) for $C_{16}H_{17}FN_4O_4$

NMR (DMSO-D6) δ: 1.84 (s, 3H); 3.37 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.39 (s, 2H); 4.77 (m, 1H); 4.97 (brs, 1H); 7.34 (s, 1H); 7.45 (dm, 1H); 7.66 (t, 1H); 7.71 (dd, 1H); 7.91 (t, 1H); 8.22 (brt, 1H).

Example 2: N-[(5S)-3-(3-Fluoro-4-(4-(1-methylimidazole-2-thiomethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

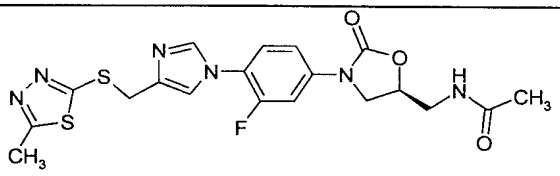
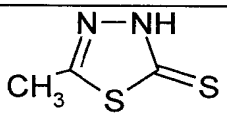
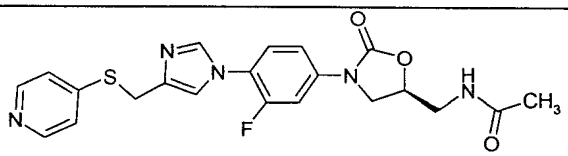
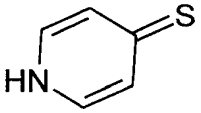
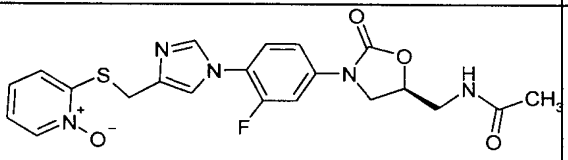
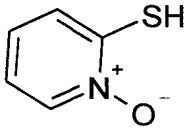
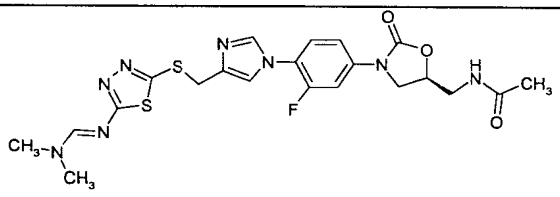
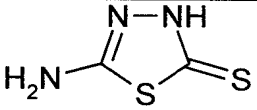
The title product (200 mg) was prepared as Example 1, but starting from 1-methylimidazole-2-thione (228 mg, 2 mM), and heating for 2 hours.

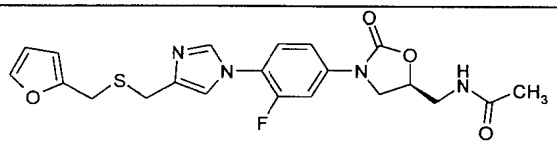
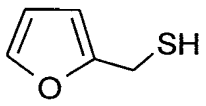
MS (ESP): 445 (MH^+) for $C_{20}H_{21}FN_6O_3S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.41 (t, 2H); 3.47 (s, 3H); 3.76 (dd, 1H); 4.11 (s, 2H); 4.15 (t, 1H); 4.74 (m, 1H); 6.94 (d, 1H); 7.21 (m, 2H); 7.41 (dd, 1H); 7.58 (t, 1H); 7.69 (dd, 1H); 7.94 (t, 1H); 8.23 (brt, 1H).

Examples 3-7

Using essentially the method and scale of Example 1, but starting from the listed thione or thiol, and using 6 equivalents of *N,N*-dimethylformamide dineopentyl acetal, the following compounds were prepared.

Example	Product	Starting material	Foot notes
3			1
4			2
5			3
6			4

Example	Product	Starting material	Foot notes
7			5

Footnotes

1 MS (ESP): 463 (MH^+) for $C_{19}H_{19}FN_6O_3S_2$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.66 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.46 (s, 2H); 4.75 (m, 1H); 7.42 (dd, 2H); 7.49 (s, 1H); 7.64 (t, 1H); 7.71 (dd, 1H); 7.97 (s, 1H); 8.22 (brt, 1H).

2 MS (ESP): 442 (MH^+) for $C_{21}H_{20}FN_5O_3S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.12 (t, 1H); 4.28 (s, 2H); 4.75 (m, 1H); 7.37 (dd, 2H); 7.42 (dd, 1H); 7.51 (s, 1H); 7.63 (t, 1H); 7.71 (dd, 1H); 7.95 (t, 1H); 8.22 (brt, 1H); 8.35 (d, 2H).

3 MS (ESP): 458 (MH^+) for $C_{21}H_{20}FN_5O_4S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.17 (s, 2H); 4.75 (m, 1H); 7.17 (td, 1H); 7.34 (td, 1H); 7.42 (dd, 1H); 7.53 (s, 1H); 7.63 (t, 1H); 7.65 (dd, 1H); 7.71 (dd, 1H); 7.96 (t, 1H); 8.21 (brt, 1H); 8.27 (dd, 1H).

4 8 Equivalents of N,N-dimethylformamide dineopentyl acetal used.

MS (ESP): 519 (MH^+) for $C_{21}H_{23}FN_8O_3S_2$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.96 (s, 3H); 3.10 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.22 (s, 2H); 4.74 (m, 1H); 7.42 (dd, 1H); 7.45 (s, 1H); 7.63 (t, 1H); 7.71 (dd, 1H); 7.95 (t, 1H); 8.15 (s, 1H); 8.22 (brt, 1H).

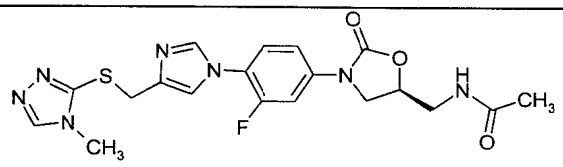
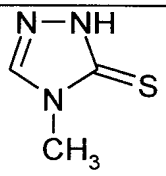
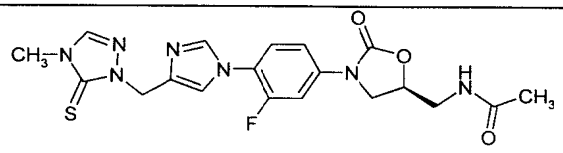
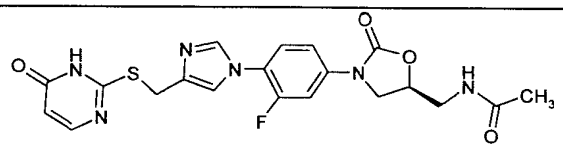
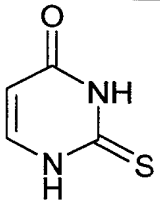
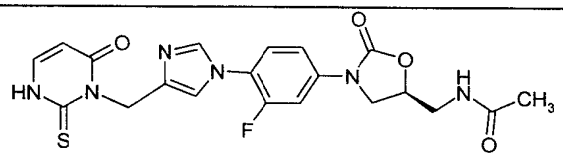
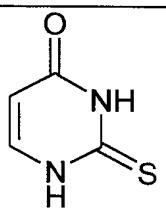
5 3 Equivalents of N,N-dimethylformamide dineopentyl acetal used, and chromatography gradient from 0 to 10% methanol in dichloromethane.

MS (ESP): 445 (MH^+) for $C_{21}H_{21}FN_4O_4S$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.41 (t, 2H); 3.63 (s, 2H); 3.77 (dd, 1H); 3.80 (s, 2H); 4.16 (t, 1H); 4.74 (m, 1H); 6.29 (m, 1H); 6.37 (m, 1H); 7.38 (s, 1H); 7.43 (dd, 1H); 7.57 (d, 1H); 7.66 (t, 1H); 7.71 (dd, 1H); 7.92 (m, 1H); 8.23 (brt, 1H).

Examples 8-11

Using essentially the method and scale of Example 1, but starting from the listed thione, and using 6 equivalents of *N,N*-dimethylformamide dineopentyl acetal, the following compounds were prepared. Separation of the isomers was achieved by chromatography on silica Mega Bond Elut® columns, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane.

Example	Product	Starting material	Foot notes
8			1
9			2
10			3
11			4

Footnotes

1 Isolated ratio of S : N substitution 8 : 1

MS (ESP): 446 (MH^+) for $C_{19}H_{20}FN_7O_3S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.48 (s, 3H); 3.76 (dd, 1H); 4.15 (t, 1H); 4.25 (s, 2H); 4.75 (m, 1H); 7.33 (s, 1H); 7.42 (dd, 1H); 7.60 (t, 1H); 7.71 (dd, 1H); 7.93 (s, 1H); 8.21 (brt, 1H); 8.52 (s, 1H).

2 MS (ESP): 446 (MH^+) for $C_{19}H_{20}FN_7O_3S$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 3.60 (s, 3H); 3.68 (dd, 1H); 3.82 (dd, 2H); 4.07 (t, 1H); 4.82 (m, 1H); 5.42 (s, 2H); 6.13 (brt, 1H); 7.26 (dd, 1H); 7.34 (t, 1H); 7.36 (s, 1H); 7.67 (dd, 1H); 7.72 (t, 1H); 7.78 (s, 1H).

3 Isolated ratio of S : N substitution 2 : 1

MS (ESP): 459 (MH^+) for $C_{20}H_{19}FN_6O_4S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.34 (s, 2H); 4.74 (m, 1H); 6.09 (d, 1H); 7.42 (dd, 1H); 7.46 (s, 1H); 7.63 (t, 1H); 7.71 (dd, 1H); 7.88 (d, 1H); 7.94 (t, 1H); 8.21 (brt, 1H).

4 MS (ESP): 459 (MH^+) for $C_{20}H_{19}FN_6O_4S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 1H); 5.34 (s, 2H); 5.95 (d, 1H); 7.42 (dd, 1H); 7.53 (s, 1H); 7.65 (t, 1H); 7.71 (dd, 1H); 7.89 (d, 1H); 7.98 (s, 1H); 8.22 (brt, 1H); 12.56 (br, 1H).

Example 12: N-[(5S)-3-(3-Fluoro-4-(4-(1-methylimidazole-2-sulfonylmethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(1-methylimidazole-2-thiomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (53 mg, 0.12 mM) was dissolved in dichloromethane (10 ml), *m*-chloroperbenzoic acid (50% strength, 83 mg, 0.24 mM) added, and the mixture stirred at ambient temperature for 17 hours. The mixture was diluted with an equal volume of dichloromethane, and washed with sufficent 5% aqueous sodium bicarbonate to remove all

acids. The organic phase was dried over magnesium sulfate, evaporated, and the residue dissolved in dichloromethane and chromatographed on a 5 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (20 mg).

MS (ESP): 477 (MH^+) for $C_{20}H_{21}FN_6O_5S$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 3.69 (t, 2H); 3.73 (s, 3H); 3.86 (dd, 1H); 4.08 (t, 1H); 4.71 (s, 2H); 4.83 (m, 1H); 6.43 (brt, 1H); 6.97 (s, 1H); 7.14 (s, 1H); 7.19 (s, 1H); 7.28 (dd, 1H); 7.33 (t, 1H); 7.67 (s, 1H); 7.71 (dd, 1H).

Example 13: N-[(5S)-3-(3-Fluoro-4-(4-(2-Furoyloxymethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (174 mg, 0.5 mM) and furan-2-carboxylic acid (168 mg, 1.5 mM) were suspended in dry dichloromethane (20 ml) under argon, and *N,N*-dimethylformamide dineopentyl acetal (462 mg, 2 mM) added. The mixture was stirred at ambient temperature for 48 hours giving a solution. The mixture was diluted with an equal volume of dichloromethane, and washed with sufficent 5% aqueous sodium bicarbonate to remove all acids. The organic phase was dried over magnesium sulfate, evaporated, and the residue dissolved in dichloromethane and chromatographed on a 5 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (184 mg).

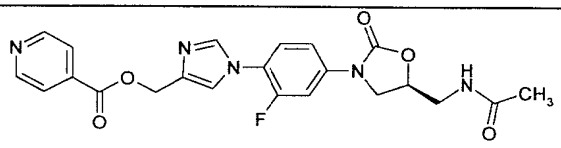
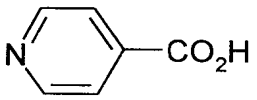
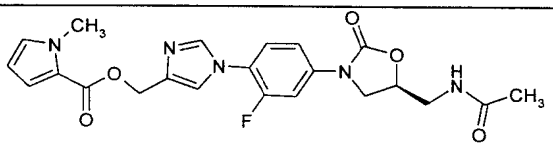
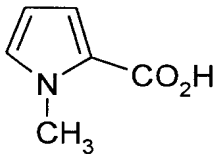
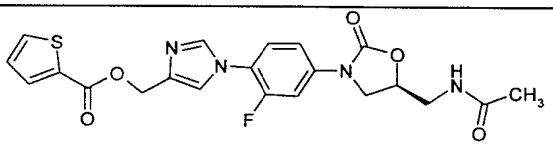
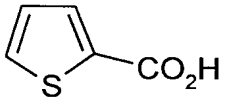
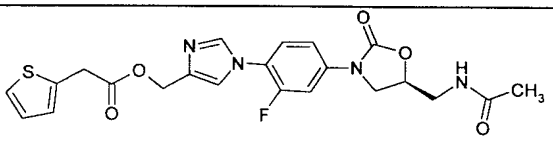
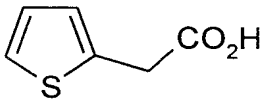
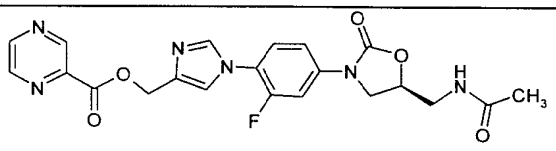
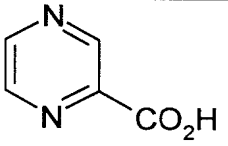
MS (ESP): 443 (MH^+) for $C_{21}H_{19}FN_4O_6$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.75 (m, 1H); 5.22 (s, 2H); 6.67 (dd, 1H); 7.31 (d, 1H); 7.40 (dd, 1H); 7.63 (s, 1H); 7.67 (t, 1H); 7.72 (dd, 1H); 7.94 (d, 1H); 8.02 (t, 1H); 8.23 (brt, 1H).

Examples 14-18

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (139 mg, 0.4 mM) and the listed carboxylic acid (0.5 mM) were suspended in dry dichloromethane (5 ml) under argon, and *N,N*-dimethylformamide dineopentyl acetal (185 mg, 0.8 mM) added. The mixture was stirred at ambient temperature for 48 hours giving

a solution. The mixture was applied directly to a 10 g silica Mega Bond Elut® column, and eluted with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give products.

Example	Product	Starting material	Foot notes
14			1
15			2
16			3
17			4
18			5

1 MS (ESP): 454 (MH^+) for $C_{22}H_{20}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.75 (m, 1H); 5.31 (s, 2H); 7.44 (dd, 1H); 7.67 (t, 1H); 7.69 (s, 1H); 7.73 (dd, 1H); 7.83 (d, 2H); 8.02 (s, 1H); 8.22 (brt, 1H); 8.78 (d, 2H).

2 Tetramethylguanidine (0.15 ml) added to give complete solution before final column. MS (ESP): 456 (MH^+) for $C_{22}H_{22}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 3.84 (s, 3H); 4.15 (t, 1H); 4.74 (m, 1H); 5.14 (s, 2H); 6.06 (m, 1H); 6.82 (m, 1H); 7.07 (m, 1H); 7.43 (dd, 1H); 7.59 (s, 1H); 7.66 (t, 1H); 7.72 (dd, 1H); 7.92 (s, 1H); 8.21 (brt, 1H).

3 MS (ESP): 459 (MH^+) for $C_{21}H_{19}FN_4O_5S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.44 (t, 2H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.78 (m, 1H); 5.23 (s, 2H); 7.19 (t, 1H); 7.43 (dd, 1H); 7.63 (s, 1H); 7.67 (t, 1H); 7.72 (dd, 1H); 7.80 (d, 1H); 7.93 (d, 1H); 8.00 (s, 1H); 8.22 (brt, 1H).

4 Tetramethylguanidine (0.15 ml) added to give complete solution before final column.

MS (ESP): 473 (MH^+) for $C_{22}H_{21}FN_4O_5S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 3.93 (s, 2H); 4.15 (t, 1H); 4.74 (m, 1H); 5.05 (s, 2H); 6.95 (m, 2H); 7.38 (m, 1H); 7.43 (dd, 1H); 7.54 (s, 1H); 7.64 (t, 1H); 7.72 (dd, 1H); 7.97 (s, 1H); 8.21 (brt, 1H).

5 MS (ESP): 455 (MH^+) for $C_{21}H_{19}FN_6O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.74 (m, 1H); 5.34 (s, 2H); 7.43 (dd, 1H); 7.67 (t, 1H); 7.70 (s, 1H); 7.77 (dd, 1H); 8.02 (s, 1H); 8.21 (brt, 1H); 8.79 (m, 1H); 8.87 (d, 1H); 9.21 (d, 1H).

Example 19: N-[(5S)-3-(3-Fluoro-4-(4-(4-methyl-5-nitropyridin-2-yl)aminomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-aminomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (80 mg, 0.23 mM), 2-chloro-4-methyl-5-nitropyridine (80 mg, 0.46 mM) and triethylamine (1 ml) in acetonitrile (4 ml) under argon, were refluxed for 17 hours. Solvent was evaporated, and the residue dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (77 mg).

MS (ESP): 484 (MH^+) for $C_{22}H_{22}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.44 (s, 3H); 3.40 (t, 2H); 3.74 (dd, 1H); 4.13 (t, 1H); 4.48 (brd, 2H); 4.74 (m, 1H); 6.46 (s, 1H); 7.39 (s, 1H); 7.42 (dd, 1H); 7.61 (t, 1H); 7.70 (dd, 1H); 7.95 (s, 1H); 8.16 (brq, 1H); 8.20 (brt, 1H); 8.81 (s, 1H).

The intermediate for this compound was prepared as follows.

N-[(5S)-3-(3-Fluoro-4-(4-azidomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (1.74 g, 5 mM) was suspended in dry dichloromethane (60 ml), diphenylphosphoryl azide (2.47 g, 9 mM) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.82 g, 12 mM) added, and the mixture stirred under argon at ambient temperature for 48 hours. The resulting solution was columned on silica (75 g) through a sinter funnel, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (1.76 g).

MS (ESP): 374 (MH^+) for $C_{16}H_{16}FN_7O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.32 (s, 2H); 4.76 (m, 1H); 7.44 (dd, 1H); 7.58 (s, 1H); 7.67 (t, 1H); 7.72 (dd, 1H); 8.02 (s, 1H); 8.22 (brt, 1H).

N-[(5S)-3-(3-Fluoro-4-(4-aminomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide

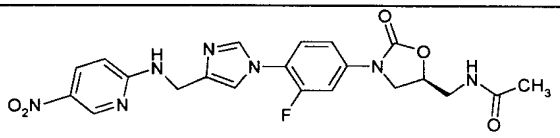
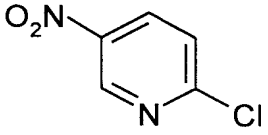
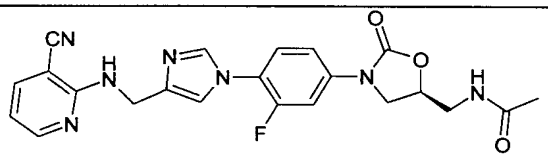
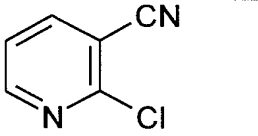
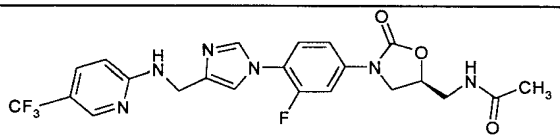
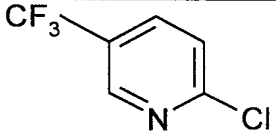
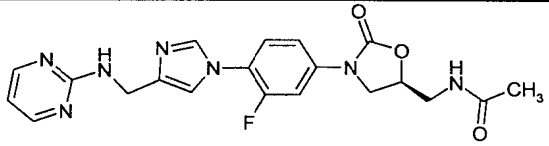
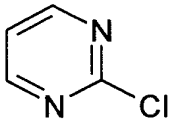
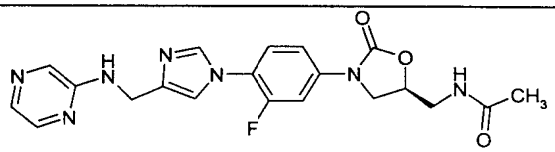
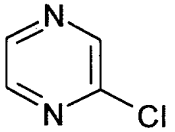
N-[(5S)-3-(3-Fluoro-4-(4-azidomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (1.38 g, 3.67 mM) was dissolved in ethanol (60 ml), treated with Lindlar catalyst (5% Pd on $CaCO_3$ partially poisoned with lead, 650 mg), and stirred under an atmosphere of hydrogen under balloon pressure for 4 hours. After filtration through celite, solvent was evaporated to give the title product as a gum, pure enough for further work (1.3 g).

MS (ESP): 348 (MH^+) for $C_{16}H_{18}FN_5O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.40 (t, 2H); 3.62 (s, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.76 (m, 1H); 7.27 (s, 1H); 7.41 (dd, 1H); 7.61 (t, 1H); 7.69 (dd, 1H); 7.88 (s, 1H); 8.22 (brt, 1H).

Examples 20-24

N-[(5S)-3-(3-Fluoro-4-(4-aminomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (104 mg, 0.3 mM), triethylamine (0.1 ml. 0.718 mM) and the listed chloroheterocycle (0.45 mM) were heated in *N*,*N*-dimethylacetamide (1 ml) at 100° for 17 hours. The residue was dissolved in dichloromethane (80 ml), washed with dilute aqueous sodium bicarbonate (2 x 20 ml), and dried over sodium sulfate. The filtered solution was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give product.

Example	Product	Starting material	Foot notes
20			1
21			2
22			3
23			4
24			5

1 MS (ESP): 470 (MH^+) for $C_{21}H_{20}FN_7O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.15 (t, 1H); 4.53 (brs, 2H); 4.74 (m, 1H); 6.65 (d, 1H); 7.42 (dd, 1H); 7.44 (s, 1H); 7.63 (t, 1H); 7.71 (dd, 1H); 7.97 (t, 1H); 8.10 (dd, 1H); 8.22 (brt, 1H); 8.43 (brt, 1H); 8.92 (d, 1H).

2 MS (ESP): 450 (MH^+) for $C_{22}H_{20}FN_7O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.75 (dd, 1H); 4.13 (t, 1H); 4.52 (d, 2H); 4.75 (m, 1H); 6.65 (dd, 1H); 7.26 (brt, 1H); 7.30 (s, 1H); 7.40 (dd, 1H); 7.61 (t, 1H); 7.69 (dd, 1H); 7.89 (dd, 1H); 7.92 (m, 1H); 8.22 (brt, 1H); 8.27 (dd, 1H).

3 MS (ESP): 493 (MH^+) for $C_{22}H_{20}F_4N_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.44 (d, 2H); 4.75 (m, 1H); 6.66 (dd, 1H); 7.38 (s, 1H); 7.42 (dd, 1H); 7.62 (overlapping m, 3H); 7.71 (dd, 1H); 7.95 (s, 1H); 8.22 (brt, 1H); 8.27 (s, 1H).

4 Chromatography gradient from 0 to 20% methanol in dichloromethane.

MS (ESP): 426 (MH^+) for $C_{20}H_{20}FN_7O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.75 (dd, 1H); 4.14 (t, 1H); 4.40 (d, 2H); 4.74 (m, 1H); 6.56 (t, 1H); 7.28 (s, 1H); 7.32 (brt, 1H); 7.41 (dd, 1H); 7.61 (t, 1H); 7.69 (dd, 1H); 7.91 (t, 1H); 8.21 (brt, 1H); 8.26 (d, 2H).

5 MS (ESP): 426 (MH+) for $C_{20}H_{20}FN_7O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 3.68 (t, 2H); 3.85 (dd, 1H); 4.08 (t, 1H); 4.56 (d, 2H); 4.82 (m, 1H); 5.36 (br, 1H); 6.29 (brt, 1H); 7.17 (s, 1H); 7.25 (dd, 1H); 7.34 (t, 1H); 7.68 (dd, 1H); 7.71 (s, 1H); 7.80 (d, 1H); 7.97 (s, 1H); 8.02 (d, 1H).

Example 25: N-[(5S)-3-(3-Fluoro-4-(4-benzimidazol-1-ylmethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (104 mg, 0.3 mM) and benzimidazole (71 mg, 0.6 mM) were suspended in dry acetonitrile (6 ml) under argon, and *N,N*-dimethylformamide dineopentyl acetal (208 mg, 0.9 mM) added. The mixture was refluxed for 8 hours. Solvent was evaporated, and the residue dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut®

column, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (50 mg).

MS (ESP): 449 (MH^+) for $C_{23}H_{21}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.75 (m, 1H); 5.39 (s, 2H); 7.18 (m, 2H); 7.41 (dd, 1H); 7.60-7.75 (overlapping m, 5H); 7.94 (s, 1H); 8.21 (brt, 1H); 8.28 (s, 1H).

Example 26: N-[(5S)-3-(3-Fluoro-4-(4-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)methylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-azidomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (200 mg, 0.54 mM) and ethyl propiolate (79 mg, 0.81 mM) were dissolved in acetonitrile (10 ml) and heated under reflux for 3 hours. Further ethyl propiolate (79 mg) was added, and heting continued for a total of 7 hours. Solvent was evaporated, the residue dissolved in the minimum volume of dichloromethane, and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (184 mg), containing about 10% of the 5-ethoxycarbonyl isomer.

MS (ESP): 472 (MH^+) for $C_{21}H_{22}FN_7O_5$

NMR (DMSO-D6) δ: 1.28 (t, 3H); 1.82 (s, 3H); 3.42 (t, 2H); 3.77 (dd, 1H); 4.14 (t, 1H); 4.28 (q, 2H); 4.75 (m, 1H); 5.59 (s, 2H); 7.44 (dd, 1H); 7.64 (overlapping m, 2H); 7.73 (dd, 1H); 8.00 (t, 1H); 8.22 (brt, 1H); 8.71 (s, 1H).

Example 27: N-[(5S)-3-(3-Fluoro-4-(4-(4-aminocarbonyl-1,2,3-triazol-1-yl)methylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

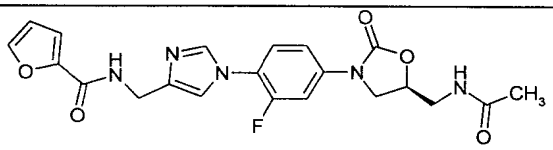
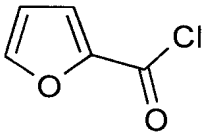
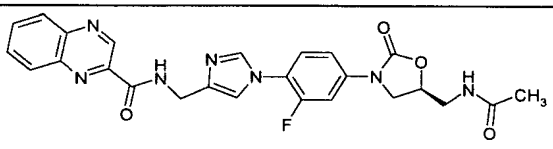
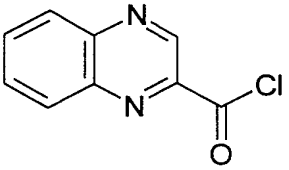
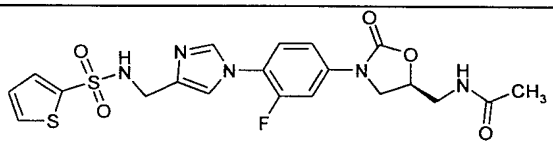
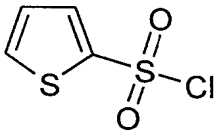
N-[(5S)-3-(3-Fluoro-4-(4-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)methylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (64 mg, 0.14 mM) was dissolved in methanol (10 ml) and concentrated aqueous ammonia solution (5 ml) added. The mixture was allowed to stand at ambient temperature for 12 hours, then evaporated to dryness to give the title product (54 mg).

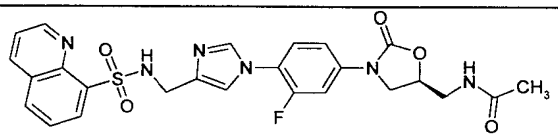
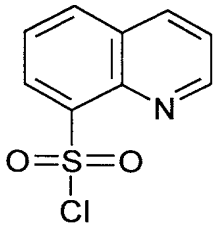
MS (ESP): 443 (MH^+) for $C_{19}H_{19}FN_8O_4$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.40 (t, 2H); 3.76 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 1H); 5.56 (s, 2H); 7.40 (overlapping m, 2H); 7.64-7.80 (overlapping m, 4H); 8.00 (s, 1H); 8.21 (brt, 1H); 8.46 (s, 1H).

Examples 28-31

N-[(5S)-3-(3-Fluoro-4-(4-aminomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (104 mg, 0.33 mM) was suspended in dry dichloromethane (5 ml) under argon. Triethylamine (0.1 ml, 0.72 mM) was added followed by the appropriate acyl or sulfonyl chloride (0.4 mM) and the mixture stirred at ambient temperature for 1 hour. The solution was chromatographed directly on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated, taken up in dichloromethane (50 ml), and washed with aqueous 5% sodium bicarbonate before drying over magnesium sulfate to give the products after evaporation.

Example	Product	Starting material	Foot notes
28			1
29			2
30			3

Example	Product	Starting material	Foot notes
31			4

1 MS (ESP): 442 (MH^+) for $C_{21}H_{20}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.74 (dd, 1H); 4.12 (t, 1H); 4.36 (d, 2H); 4.74 (m, 1H); 6.59 (dd, 1H); 7.13 (d, 1H); 7.32 (s, 1H); 7.41 (dd, 1H); 7.62 (t, 1H); 7.70 (dd, 1H); 7.79 (d, 1H); 7.92 (d, 1H); 8.24 (brt, 1H);); 8.67 (brt, 1H).

2 MS (ESP): 504 (MH^+) for $C_{25}H_{22}FN_7O_4$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.40 (t, 2H); 3.75 (dd, 1H); 4.14 (t, 1H); 4.53 (d, 2H); 4.74 (m, 1H); 7.41 (overlapping m, 2H); 7.63 (t, 1H); 7.71 (dd, 1H); 7. 97 (overlapping m, 3H); 8.19 (overlapping m, 3H); 9.22 (brt, 1H); 9.47 (s, 1H)

3 MS (ESP): 494 (MH^+) for $C_{20}H_{20}FN_5O_5S_2$

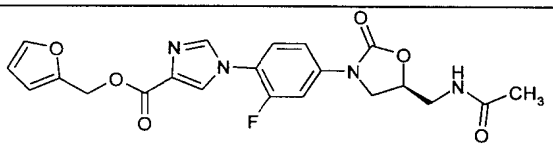
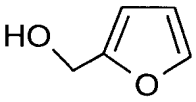
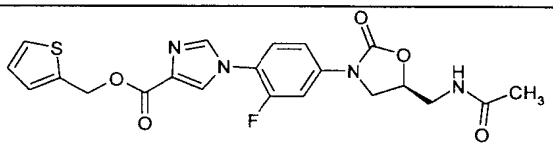
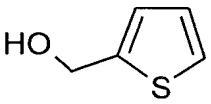
NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.75 (dd, 1H); 4.01 (d, 2H); 4.15 (t, 1H); 4.75 (m, 1H); 7.12 (dd, 1H); 7.24 (s, 1H); 7.42 (dd, 1H); 7.56 (t overlapping m, 2H); 7.71 (dd, 1H); 7.88 (overlapping m, 2H); 8.22 (overlapping m, 2H).

4 MS (ESP): 539 (MH^+) for $C_{25}H_{23}FN_6O_5S$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.41 (t, 2H); 3.75 (dd, 1H); 4.03 (d, 2H); 4.14 (t, 1H); 4.75 (m, 1H); 6.99 (s, 1H); 7.14 (overlapping m, 3H); 7.56 (t, 1H); 7.68 (overlapping m, 3H); 8.20 (overlapping m, 3H); 8.48 (dd, 1H); 9.02 (m, 1H).

Examples 32-34

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (181 mg, 0.5 mM) and the listed alcohol (1.5 mM) were suspended in dry acetonitrile (2 ml), and *N,N*-dimethylformamide dineopentyl acetal (347 mg, 1.5 mM) added. The mixture was heated with stirring at 80° for 17 hours, cooled, solvent evporated, the residue dissolved in dichloromethane (50 ml), and washed with sufficient aqueous sodium bicarbonate to remove acid. After drying (magnesium sulfate) and evaporation to a suitable volume, the solution was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the products.

Example	Product	Starting material	Foot notes
32			1
33			2
34	There is no Example 34		

1 MS (ESP): 443 (MH^+) for $C_{21}H_{19}FN_4O_6$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 1H); 5.25 (s, 2H); 6.47 (m, 1H); 6.57 (d, 1H); 7.43 (dd, 1H); 7.68 (d, 1H); 7.69 (t, 1H); 7.71 (dd, 1H); 8.11 (m, 1H); 8.21 (brt, 1H);); 8.25 (d, 1H).

2 MS (ESP): 459 (MH^+) for $C_{21}H_{19}FN_4O_5S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 1H); 5.45 (s, 2H); 7.02 (dd, 1H); 7.22 (d, 1H); 7.43 (dd, 1H); 7.55 (d, 1H); 7.71 (t, 1H); 7.74 (dd, 1H); 8.11 (s, 1H); 8.21 (brt, 1H);); 8.25 (s, 1H).

The intermediate for this compound was prepared as follows.

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

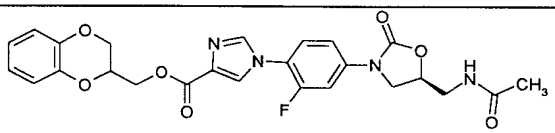
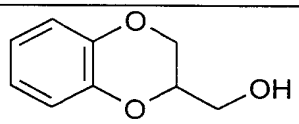
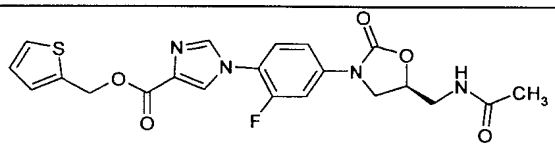
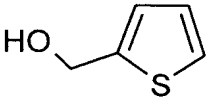
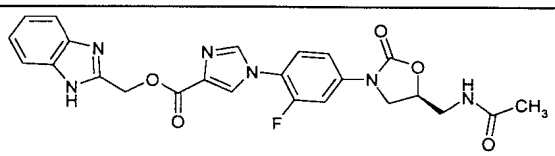
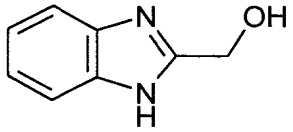
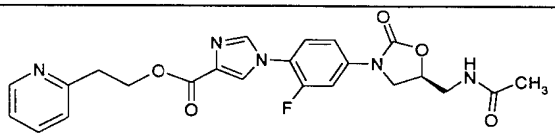
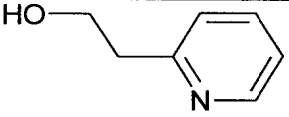
N-[(5S)-3-(3-Fluoro-4-(4-hydroxymethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (9.74 g, 28 mM) and triethylamine (28.3 g, 0.28 M) were stirred in dimethylsulfoxide (70 ml) under argon at ambient temperature. A solution of pyridine-sulfur trioxide complex (13.4 g, 84 mM) in dimethylsulfoxide (70 ml) was added dropwise over 10 minutes, maintaining the temperature at ~20°C. Stirrring was continued for a further 1 hour to give a solution of N-[(5S)-3-(3-fluoro-4-(4-aldehydoimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide. This was treated with ice-water (70 ml) and then acidified gradually with phosphoric acid (85%, 49g), with cooling. The resulting suspension was then stirred at 20°, and a solution of sodium chlorite (5.04 g, 56 mM) in water (70 ml) added dropwise over 2 hours, before finally stirring 18 hours at ambient temperature. After dilution with ice water (1.4 l), the mixture was stirred 1 hour, the resulting precipitate filtered, washed with water (2 x 50 ml) and dried to give title product (8.2 g).

MS (Negative ESP): 361 (MH^-) for $C_{16}H_{15}FN_4O_5$

NMR (DMSO-D6 + TFA) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.47 (dd, 1H); 7.74, 7.78 (t overlapping dd, 2H); 8.23 (t, 1H); 8.42 (s, 1H); 8.82 (s, 1H).

Examples 35-38

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (181 mg, 0.5 mM), the listed alcohol (1 mM), 4-dimethylaminopyridine (30 mg, 0.25 mM) and dicyclohexylcarbodiimide (206 mg, 1 mM) were dissolved in *N,N*-dimethylformamide (2 ml), and stirred under argon for 17 hours. The mixture was diluted with dichloromethane (20 ml), washed with aqueous sodium dihydrogen phosphate (2M, 10 ml) and water (10 ml). After drying (magnesium sulfate) and evaporation to a suitable volume, the solution was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the products.

Example	Product	Starting material	Foot notes
35			1
36			2
37			3
38			4

1 MS (ESP): 443 (MH^+) for $C_{25}H_{23}FN_4O_7$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.15 (t overlapping m, 2H); 4.37-4.54 (complex m, 4H); 4.75 (m, 1H); 6.85 (m, 4H); 7.45 (dd, 1H); 7.71 (t, 1H); 7.74 (dd, 1H); 8.12 (s, 1H); 8.21 (brt, 1H); 8.28 (s, 1H).

2 MS (ESP): 506 (MH^+) for $C_{26}H_{24}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.09 (t, 2H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.42 (t, 2H); 4.75 (m, 1H); 6.96 (t, 1H); 7.05 (t, 1H); 7.23 (d, 1H); 7.27 (d, 1H); 7.45 (dd, 1H); 7.59 (d, 1H); 7.72 (t, 1H); 7.76 (dd, 1H); 8.11 (s, 1H); 8.19 (s, 1H); 8.23 (brt, 1H); 10.84 (br, 1H).

3 After dilution of the reaction mixture with water and dichloromethane, the product precipitated, and was filtered and washed with acetone.

MS (ESP): 493 (MH^+) for $C_{24}H_{21}FN_6O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.41 (t, 2H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 1H); 6.47 (s, 2H); 7.16 (m, 2H); 7.42 (dd, 1H); 7.52 (m, 2H); 7.73 (t, 1H); 7.75 (dd, 1H); 8.16 (s, 1H); 8.22 (brt, 1H); 8.35 (s, 1H); 12.57 (br, 1H).

4 MS (ESP): 468 (MH^+) for $C_{23}H_{22}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.13 (t, 2H); 3.41 (t, 2H); 3.76 (dd, 1H); 4.16 (t, 1H); 4.56 (t, 2H); 4.75 (m, 1H); 7.21 (dd, 1H); 7.34 (d, 1H); 7.45 (dd, 1H); 7.70 (overlapping m, 3H); 8.08 (s, 1H); 8.14 (s, 1H); 8.22 (brt, 1H); 8.49 (d, 1H).

Example 39: N-[(5S)-3-(3-Fluoro-4-(4-(4-morpholinocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(4-nitrophenoxycarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (170 mg, 0.35 mM) was dissolved in dichloromethane (20 ml) and morpholine (61 mg, 0.7 mM) added. The mixture was stirred at ambient temperature for 17 hours, and the solution chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (114 mg).

MS (ESP): 432 (MH^+) for $C_{20}H_{22}FN_5O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.40 (t, 2H); ~3.6 (v br, 2H); 3.61 (m, 4H); 3.77 (dd, 1H); ~4.1 (v br, 2H); 4.15 (t, 1H); 4.74 (m, 1H); 7.44 (dd, 1H); 7.72 (t, 1H); 7.74 (dd, 1H); 7.98 (s, 1H); 8.07 (s, 1H); 8.22 (brt, 1H).

The intermediate for this compound was prepared as follows.

N-[(5S)-3-(3-Fluoro-4-(4-(4-nitrophenoxycarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (181 mg, 0.5 mM), 4-nitrophenol (139 mg, 1 mM), dicyclohexylcarbodiimide (144 mg, 0.7 mM) and 4-dimethylaminopyridine (61 mg, 0.5 mM) were dissolved in *N,N*-dimethylformamide (2 ml). The mixture was stirred at ambient temperature

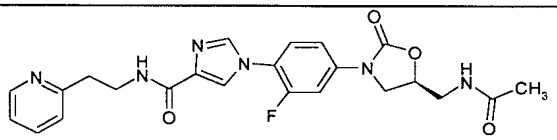
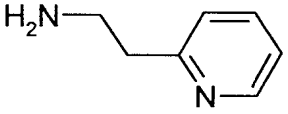
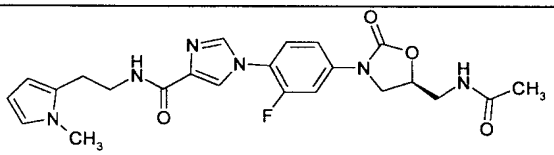
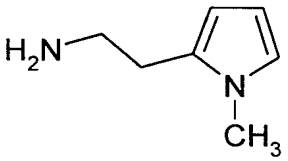
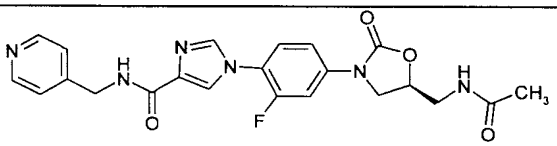
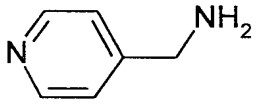
for 17 hours, diluted with dichloromethane (20 ml), washed with 1M aqueous sodium dihydrogen phosphate (10 ml), water (2 x 10 ml), and dried over magnesium sulfate. After filtration and evaporation to a suitable volume, the solution was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (210 mg).

MS (ESP): 484 (MH^+) for $C_{22}H_{18}FN_5O_7$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.18 (t, 1H); 4.77 (m, 1H); 7.48 (dd, 1H); 7.57 (d, 2H); 7.72 (t overlapping dd, 2H); 8.22 (brt, 1H); 8.25 (s, 1H); 8.32 (d, 2H); 8.59 (s, 1H).

Examples 40-42

N-[(5S)-3-(3-Fluoro-4-(4-(4-nitrophenoxycarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (193 mg, 0.4 mM) and triethylamine (50 mg, 0.5 mM) were dissolved in dichloromethane (10 ml) and the listed amine (0.5 mM) added. The mixture was stirred at ambient temperature for 17 hours, and the solution chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title products.

Example	Product	Starting material	Foot notes
40			1
41			2
42			3

1 MS (ESP): 467 (MH^+) for $C_{23}H_{23}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.97 (t, 2H); 3.41 (t, 2H); 3.61 (q, 2H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.76 (m, 1H); 7.20 (dd, 1H); 7.27 (d, 1H); 7.44 (dd, 1H); 7.70 (t overlapping m, 3H); 7.96 (s, 1H); 8.05 (s, 1H); 8.16 (brt, 1H); 8.22 (brt, 1H); 8.49 (d, 1H).

2 MS (ESP): 506 (MH^+) for $C_{23}H_{25}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.74 (t, 2H); 3.41 (t overlapping q, 4H); 3.52 (s, 3H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.75 (m, 1H); 5.81 (m, 1H); 5.85 (m, 1H); 6.58 (m, 1H); 7.44 (dd, 1H); 7.71 (t, 1H); 7.76 (m, 1H); 7.96 (s, 1H); 8.07 (s, 1H); 8.14 (brt, 1H); 8.22 (brt, 1H).

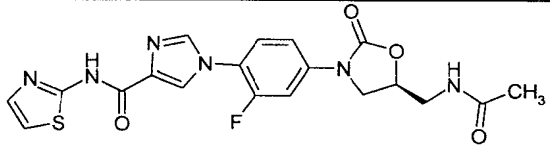
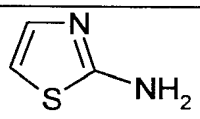
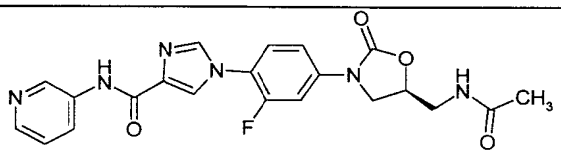
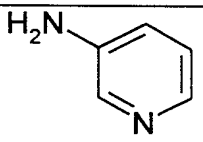
3 Solvent was acetonitrile, and reaction heated at 80° for 4 hours

MS (ESP): 506 (MH^+) for $C_{22}H_{21}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.77 (dd, 1H); 4.16 (t, 1H); 4.45 (d, 2H); 4.76 (m, 1H); 7.26 (d, 2H); 7.45 (dd, 1H); 7.72 (t, 1H); 7.76 (dd, 1H); 8.03 (d, 1H); 8.11 (t, 1H); 8.22 (brt, 1H); 8.45 (d, 2H); 8.79 (brt, 1H).

Examples 43-44

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (145 mg, 0.4 mM), and 1-hydroxybenzotriazole (67 mg, 0.5 mM) were dissolved in *N,N*-dimethylformamide (2 ml) and treated with a solution of dicyclohexylcarbodiimide (124 mg, 0.6 mM) in dichloromethane (1 ml). The mixture was stirred at ambient temperature for 2 hours, and the appropriate amine (0.5 mM) added. After stirring for 18 hours, the mixture was diluted with dichloromethane (50 ml) and shaken with dilute aqueous sodium bicarbonate (20 ml). Product precipitated and was filtered off, and washed with dichloromethane and water to give products.

Example	Product	Starting material	Foot notes
43			1
44			2

1 MS (ESP): 445 (MH^+) for $C_{19}H_{17}FN_6O_4S$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 7.24 (d, 1H); 7.51 (overlapping m, 2H); 7.76 (t overlapping dd, 2H); 8.22 (s overlapping brt, 2H) 8.41 (s, 1H); 11.67 (br, 1H)

2 Product did not precipitate, so washed with dilute aqueous sodium bicarbonate (3 x 20 ml), and the dried solution chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give product.

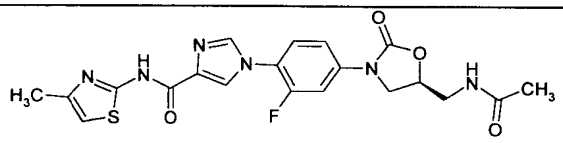
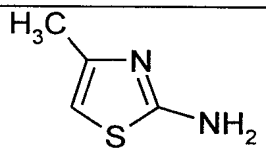
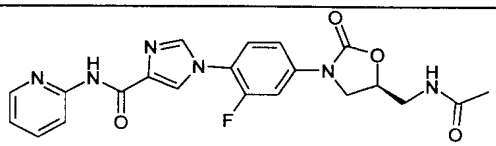
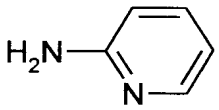
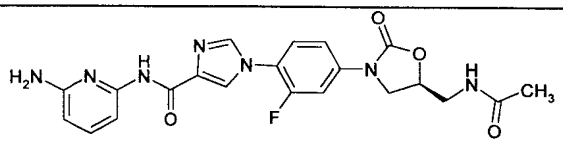
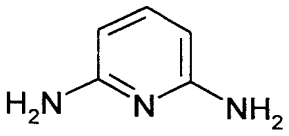
MS (ESP): 506 (MH^+) for $C_{21}H_{19}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.18 (t, 1H); 4.76 (m, 1H); 7.21 (dd, 1H); 7.47 (dd, 1H); 7.76 (t overlapping dd, 2H); 8.23 (overlapping m, 5H); 9.00 (d, 1H); 10.25 (br,1H).

Examples 45-47

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (181 mg, 0.5 mM) and 1-hydroxybenzotriazole (81 mg, 0.6 mM) were dissolved in dry *N,N*-dimethylformamide (2 ml) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (178 mg, 0.6 mM) in dichloromethane (1 ml). The mixture was stirred at ambient temperature for 2 hours, and the appropriate amine (0.5 mM) added. After stirring for 18 hours, the solvent was evaporated, and the residue stirred with a mixture of 5% aqueous sodium carbonate (2 ml), dichloromethane (5 ml) and water (3 ml). After

partial evaporation to remove dichloromethane, products were filtered and washed with water (2 x 5 ml).

Example	Product	Starting material	Foot notes
45			1
46	Chiral 		2
47			3

1 MS (ESP): 459 (MH^+) for $C_{20}H_{19}FN_6O_4S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.26 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 6.78 (s, 1H); 7.47 (dd, 1H); 7.74 (t, 1H); 7.76 (dd, 1H); 8.20, 8.22 (s overlapping brt, 2H); 8.39 (s, 1H); 11.57 (brs, 1H).

2 MS (ESP): 439 (MH^+) for $C_{21}H_{19}FN_6O_4$

NMR (DMSO-D6) δ: δ: 1.82 (s, 3H); 3.43 (t, 2H); 3.79 (dd, 1H); 4.19 (t, 1H); 4.76 (m, 1H); 7.14 (dd, 1H); 7.47 (dd, 1H); 7.77, 7.84 (overlapping m, 3H); 8.21 (s overlapping m, 3H); 8.31 (s, 1H); 8.34 (dd, 1H); 9.57 (s, 1H).

3 Excess amine (2 mM) used. Crude purified by chromatography on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 25% methanol in dichloromethane. Relevant fractions were combined and evaporated to give product.

MS (ESP): 454 (MH^+) for $C_{21}H_{20}FN_7O_4$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 5.90 (s, 2H); 6.18 (d, 1H); 7.31 (d, 1H); 7.38 (t, 1H); 7.45 (dd, 1H); 7.74, 7.84 (overlapping m, 2H); 8.16 (s, 1H); 8.21 (s overlapping m, 2H); 9.07 (s, 1H).

Example 48: N-[(5S)-3-(3-Fluoro-4-(4-(6-acetamidopyridin-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(6-aminopyridin-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (70 mg, 0.15 mM) was dissolved in pyridine (3 ml) and treated with acetic anhydride (0.5 ml). After standing 60 hours at ambient temperature, solvent was evaporated, and the residue triturated with water (10 ml). Filtration gave the title product (47 mg).

MS (ESP): 496 (MH^+) for $C_{23}H_{22}FN_7O_5$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.07 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 7.47 (dd, 1H); 7.79 (overlapping m, 5H); 8.20 (s, 1H); 8.23 (brt, 1H); 8.30 (s, 1H); 9.36 (s, 1H); 10.36 (s, 1H).

Examples 49-80

Examples 49-80 (summarised in the Table below) were prepared using the following procedure which employed a Zymark robotic system for multiple parallel synthesis.

1-Hydroxybenzotriazole ester of N-[(5S)-3-(3-fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide (25 mM) was suspended in sieve dried *N*,*N*-dimethylformamide (200 ml) and 1-hydroxybenzotriazole (30 mM) added, and the mixture cooled in an ice-bath. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide methiodide (30 mM) was added in portions over 10 minutes, and the mixture left to warm to ambient temperature over 2.5 hours.

Aliquots (4 ml) of the above stock solution were then added to the listed aminoheterocycle (0.5 mM); if the amine was as a salt, triethylamine (0.2 ml) was added prior to this addition. The mixture was then stirred at 25° for 24 hours, 55° for 12 hours, then at 25° for a further 12

hours. After dilution of samples with 5% aqueous sodium bicarbonate solution (3 ml), and stirring at 25° for 2 hours, products were filtered using a nylon filter cup and washed with an additional portion of sodium bicarbonate solution (3 ml) to give the listed products. Exceptions to this general work-up are given in the footnotes

Compounds so prepared were characterised by the presence of the correct molecular ion for MH^+ in their electrospray mass spectra, and by their HPLC retention time, using the following system and elution parameters, and in some cases by NMR.

Column HYPERSIL ODS 5m

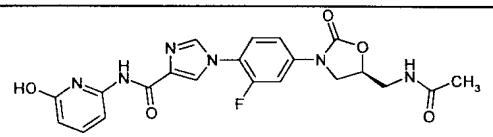
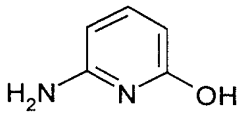
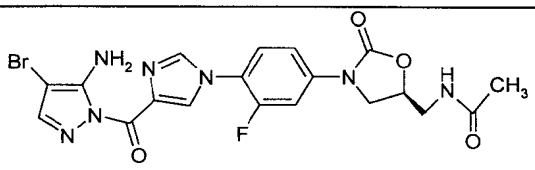
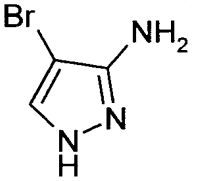
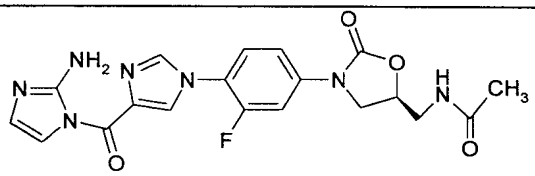
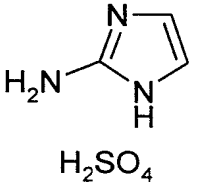
Flow rate 1.0 ml/min

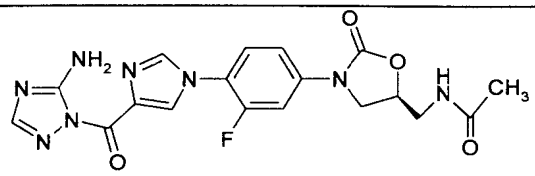
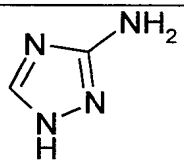
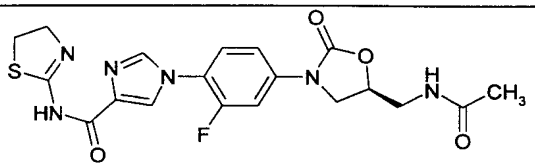
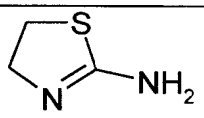
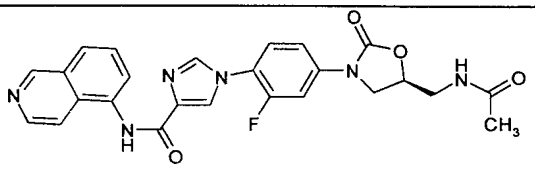
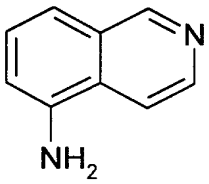
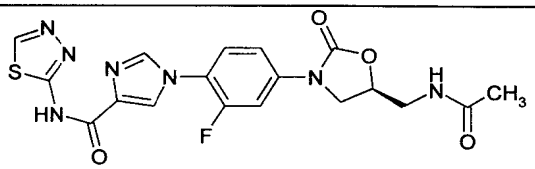
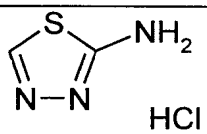
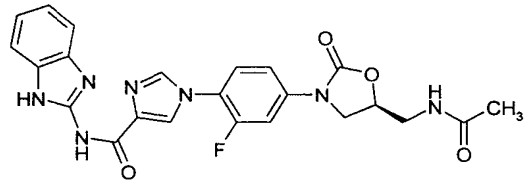
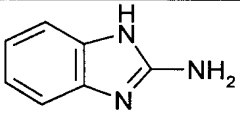
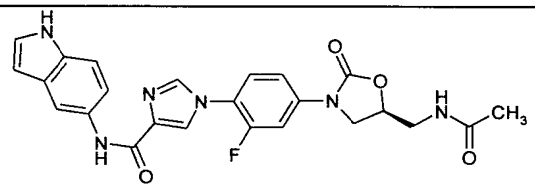
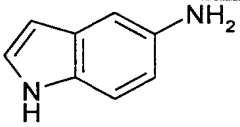
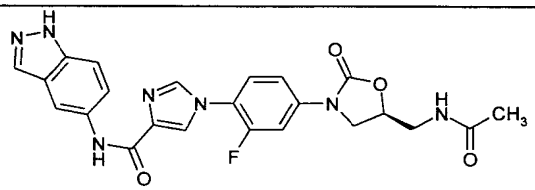
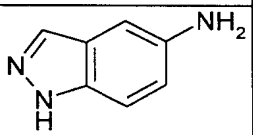
Detector Wavelength 254l

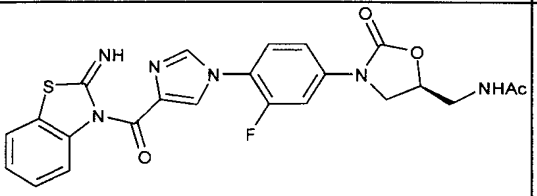
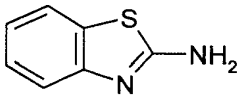
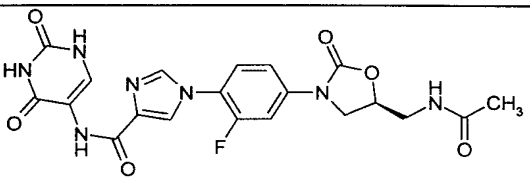
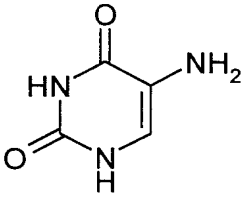
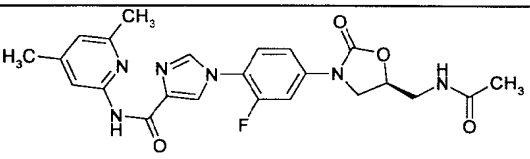
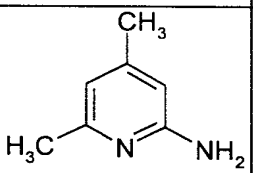
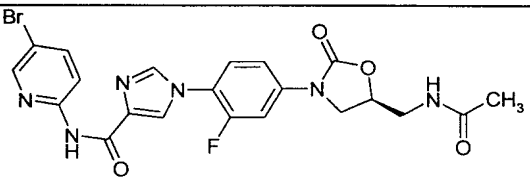
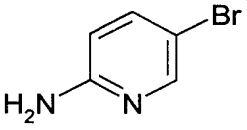
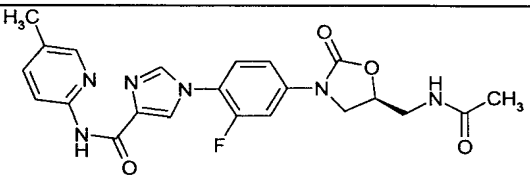
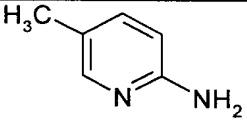
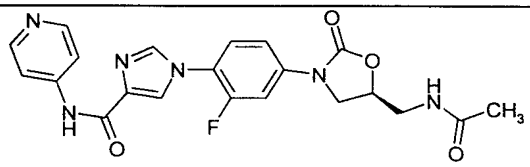
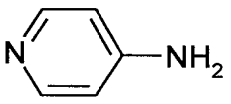
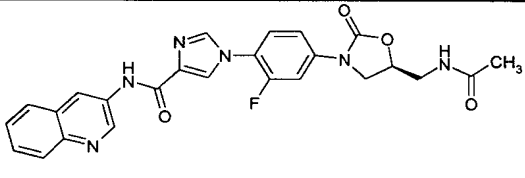
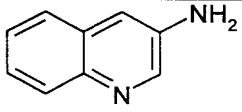
Solvent A 1 mMol TFA/H_2O

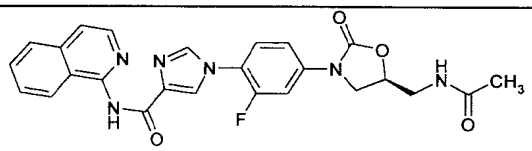
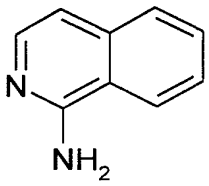
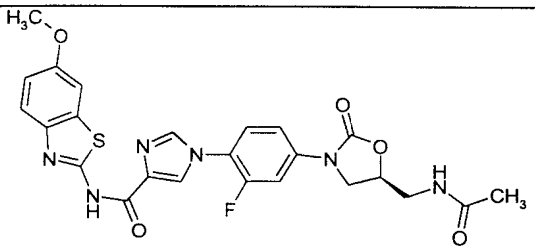
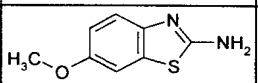
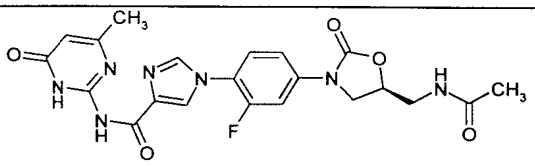
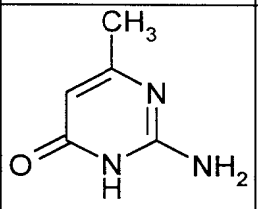
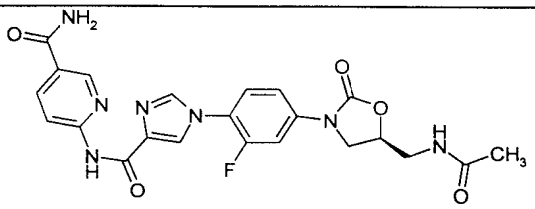
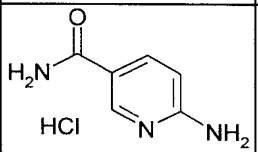
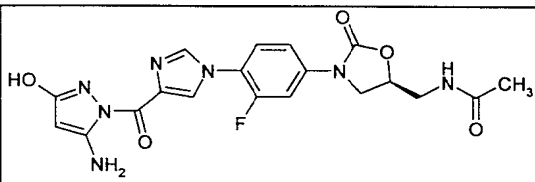
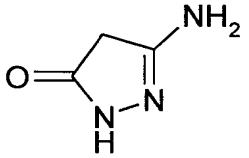
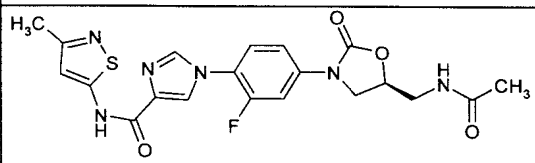
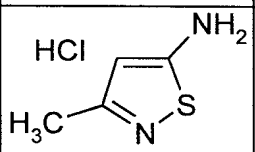
Solvent B 1 mMol TFA/CH_3CN

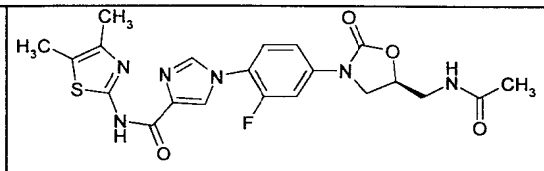
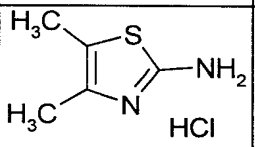
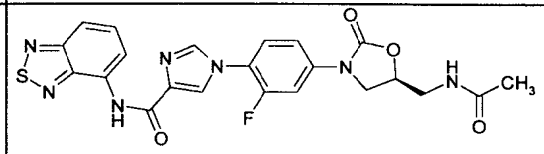
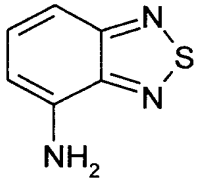
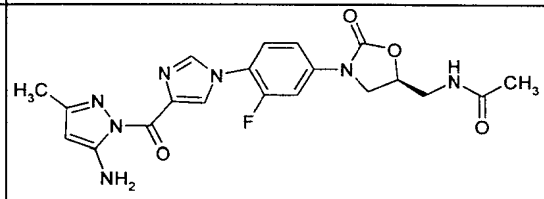
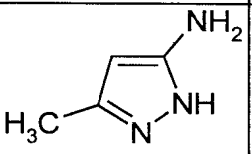
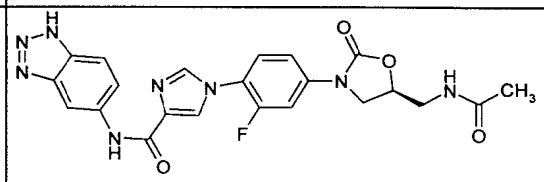
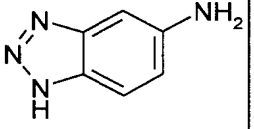
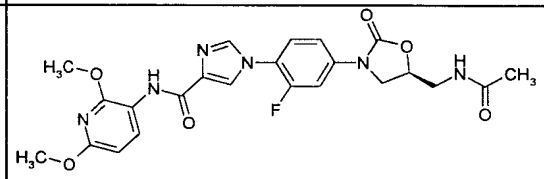
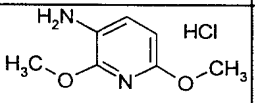
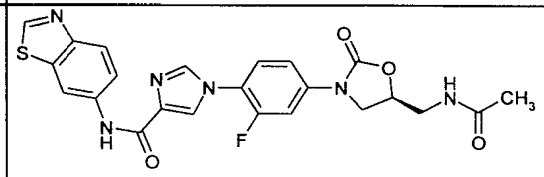
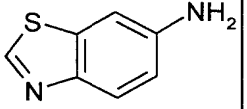
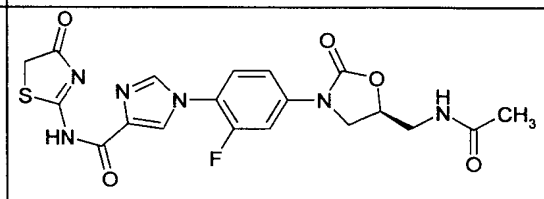
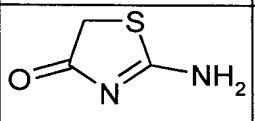
Time	*% Solvent A*	*% Solvent B*
0	95	5
3	95	5
17	5	95
18	95	5
20	95	5

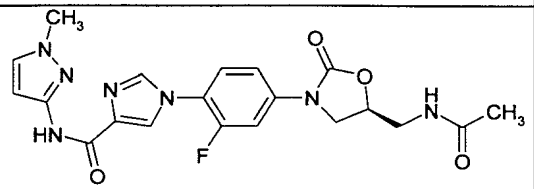
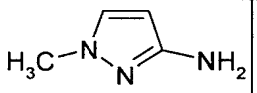
Example	Structure	Starting Material	HPLC RT	Mass Ion	Notes
49			8.74	455	
50			10.01	506	1
51			8.95	428	2

Example	Structure	Starting Material	HPLC RT	Mass Ion	Notes
52			8.77		3
53			8.94	447	4
54			9.06	489	
55			9.53	446	5
57			9.71	478	6
58			10.43	477	7
59			9.76	478	8

Example	Structure	Starting Material	HPLC RT	Mass Ion	Notes
60			11.5	495	9
61			8.71		10
62			9.61	467	
63			11.74	517	
64			9.37	453	
65			8.84	439	
66			9.74	489	

Example	Structure	Starting Material	HPLC RT	Mass Ion	Notes
67			9.87	489	
68			11.62		11
69			9.41	470	12
70			9.25	482	
71			8.80	444	13
72			9.74	459	

Example	Structure	Starting Material	HPLC RT	Mass Ion	Notes
73			10.37	473	
74			12.09	496	14
75			9.64	442	15
76			9.58		16
77			11.69	499	
78			10.56	495	
79			9.05	460	

Structure		Starting Material	HPLC	Mass	Notes
Example			RT	Ion	
80			9.35	442	17

1 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.19 (t, 1H); 4.76 (m, 1H); 5.78 (s, 2H); 7.48 (dd, 1H); 7.75 (t, 1H); 7.78 (dd, 1H); 8.21, 8.25 (s overlapping t, 2H); 8.65 (s, 2H).

2 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 6.51 (d, 1H); 6.82 (s, 2H); 7.47 (dd, 1H); 7.77 (dd, 1H); 7.79 (t, 1H); 8.21 (d, 1H); 8.24 (t, 1H); 8.28 (s, 1H); 8.53 (s, 1H).

3 NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.77 (m, 1H); 7.47 (dd, 1H); 7.66 (s, 3H); 7.78 (t overlapping dd, 2H); 8.25 (t, 1H); 8.27 (s, 1H); 8.71 (s, 1H).

4 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.16 (t, 2H); 3.40 (t, 2H); 3.67 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.44 (dd, 1H); 7.72 (t overlapping dd, 2H); 8.03 (s, 1H); 8.06 (s, 1H); 8.25 (t, 1H).

5 After reaction mixture was diluted with 5% aqueous sodium bicarbonate solution (30 ml) to precipitate the product.
NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 7.47 (dd, 1H); 7.75 (t, 1H); 7.77 (dd, 1H); 8.21 (t, 1H); 8.23 (s, 1H); 8.47 (s, 1H); 9.16 (s, 1H); 12.35 (br, 1H).

6 NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 7.03 (dd, 2H); 7.42 (dd, 2H); 7.45 (dd, 1H); 7.74 (t overlapping dd, 2H); 8.16 (s, 1H); 8.22 (t, 1H); 8.32 (s, 1H).

7 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 6.37 (d, 1H); 7.29 (m, 2H); 7.42 (d, 1H); 7.45 (dd, 1H); 7.76 (t overlapping dd, 2H); 8.01 (d, 1H); 8.13 (s, 1H); 8.17 (s, 1H); 8.24 (t, 1H); 9.67 (s, 1H); 11.05 (brs, 1H).

8 NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.47 (overlapping m, 2H); 7.69 (dd, 1H); 7.76 (t overlapping dd, 2H); 8.01 (s, 1H); 8.16 (s, 1H); 8.19 (d, 1H); 8.23 (t, 1H); 8.26 (s, 1H); 9.94 (s, 1H).

9 NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.43 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.74 (m, 1H); 7.13 (t, 1H); 7.29 (t, 1H); 7.46 (d, 1H); 7.58 (d, 1H); 7.78 (overlapping m, 3H); 8.11 (s, 1H); 8.22 (s, 1H); 8.25 (t, 1H).

10 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.40 (t, 2H); 3.79 (dd, 1H); 4.16 (t, 1H); 4.75 (m, 1H); 7.44 (dd, 1H); 7.72 (overlapping m, 2H); 8.05 (t, 1H); 8.11 (s, 1H); 8.22 (s, 1H); 8.25 (t, 1H); 9.07 (t, 1H).

11 NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.42 (t, 2H); 3.75 (s, 3H); 3.79 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 6.84 (dd, 1H); 7.32 (d, 1H); 7.39 (d, 1H); 7.46 (dd, 1H); 7.73 (t, 1H); 7.75 (dd, 1H); 8.03 (s, 2H); 8.24 (t, 1H).

12 NMR (DMSO-D6) δ: 1.82 (s, 3H); 1.99 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 5.46 (s, 1H); 7.44 (dd, 1H); 7.71 (t, 1H); 7.74 (dd, 1H); 7.93 (s, 1H); 8.00 (s, 1H); 8.27 (t, 1H).

13 NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.74 (s overlapping m, 2H); 6.64 (brs, 2H); 7.41 (dd, 1H); 7.66 (t, 1H); 7.74 (dd, 1H); 8.12 (s, 1H); 8.28 (t, 1H); 8.69 (s, 1H).

14 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.44 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.36 (d, 1H); 7.46 (dd, 1H); 7.75 (overlapping m, 3H); 8.24 (t, 1H); 8.27 (s, 1H); 8.34 (s, 1H); 8.48 (dd, 1H); 10.28 (br, 1H).

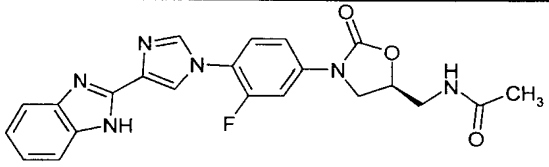
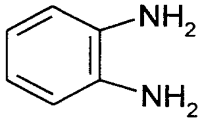
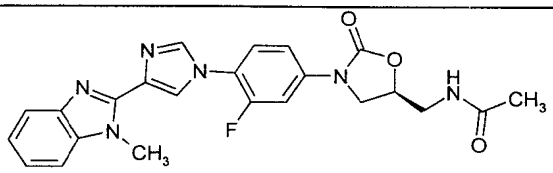
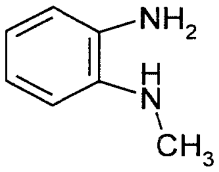
15 NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.06 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.17 (t, 1H); 4.76 (m, 1H); 5.23 (s, 1H); 6.66 (s, 2H); 7.47 (dd, 1H); 7.75 (overlapping m, 2H); 8.18 (s, 1H); 8.26 (t, 1H); 8.68 (dd, 1H).

16 NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.23 (dd, 1H); 7.45 (dd, 1H); 7.54 (d, 1H); 7.77 (overlapping m, 2H); 8.13 (m, 2H); 8.18 (s, 1H); 8.27 (t, 1H); 9.63 (s, 1H).

17 NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.66 (s, 3H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 6.18 (d, 1H); 7.29 (d, 1H); 7.46 (dd, 1H); 7.74 (t overlapping m, 2H); 8.12 (m, 1H); 8.14 (s, 1H); 8.24 (t, 1H).

Examples 81-82

N-[(5S)-3-(3-fluoro-4-(4-aldehydoimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (173 mg, 0.5 mM) was dissolved in *N,N*-dimethylformamide (4 ml) and the listed diamine (0.5 mM), followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (114 mg, 0.5 mM) added. The mixture was stirred at ambient temperature for 48 hours, then diluted with ethyl acetate (50 ml), and the precipitate filtered off. The filtrate was washed with water (50 ml), 2N sodium carbonate (50 ml), and brine (50 ml). After evporation the crude solid was dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 12% methanol in dichloromethane. Relevant fractions were combined and evaporated to give products.

Example	Product	Starting material	Foot notes
81			1
82			2

1 MS (ESP): 435 (MH^+) for $C_{22}H_{19}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.42 (t, 2H); 3.79 (dd, 1H); 4.14 (t, 1H); 4.76 (m, 1H); 7.13 (quintet, 2H); 7.46 (tm, 2H); 7.55 (m, 1H); 7.74 (m, 1H); 7.78 (t 1H); 8.19, 8.22 (2 x s overlapping m, 3H); 12.67 (s, 1H).

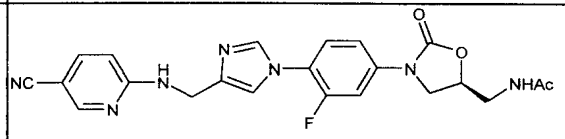
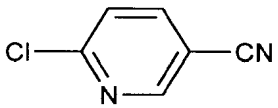
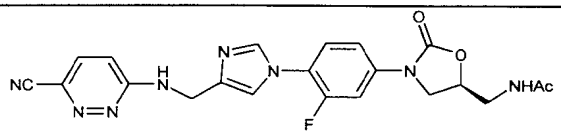
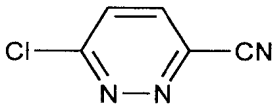
2 Work-up solvent was dichloromethane.

MS (ESP): 449 (MH^+) for $C_{23}H_{21}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.43 (t, 2H); 3.79 (dd, 1H); 4.17, 4.19 (t overlapping s, 4H); 4.75 (m, 1H); 7.20 (quintet, 2H); 7.47 (dd, 1H); 7.56 (tm, 2H); 7.74 (m, 1H); 7.79 (t 1H); 8.22 (overlapping m, 3H).

Examples 83-84 :

Using an analagous technique to that of Examples 20-24, but using acetonitrile, and heating at reflux rather than 100°, the following compounds were prepared.

Example	Product	Starting material	Foot notes
83			1
84			2

1 MS (ESP): 450 (MH^+) for $C_{22}H_{20}FN_7O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.40 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.44 (d, 2H); 4.75 (m, 1H); 6.63 (d, 1H); 7.38, 7.41 (s overlapping dd, 2H); 7.61 (t, 1H); 7.68 (overlapping m, 2H); 7.89 (br t, 1H); 7.94 (s, 1H); 8.20 (brt, 1H); 8.38 (d, 1H).

2 MS (ESP): 451 (MH^+) for $C_{21}H_{19}FN_8O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.40 (t, 2H); 3.76 (dd, 1H); 4.14 (t, 1H); 4.56 (d, 2H); 4.74 (m, 1H); 6.98 (d, 1H); 7.42 (dd, 1H); 7.45 (s, 1H); 7.62 (t, 1H); 7.70 (overlapping m, 2H); 7.96 (s, 1H); 8.16 (br, 1H); 8.20 (brt, 1H).

Example 85: N-[(5S)-3-(3-Fluoro-4-(4-(N-(pyridin-2-yl)methyl-N-methylaminocarbonyl)-imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-fluoro-4-(4-(1-benzotriazolyloxy)carbonylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (prepared as detailed for Examples 49-80; 243 mg, 0.5 mM) dissolved in DMF (4 ml) was treated with 2-(N-methylaminomethyl)pyridine (68 mg, 0.55mM). The mixture was stirred under nitrogen, and heated to 55° for 18 hours. After cooling, the mixture was diluted with saturated sodium bicarbonate solution (20 ml), extracted with ethyl acetate (2 x 10 ml), the extract washed with water and dried over magnesium sulfate. After evaporation the residue was dissolved in dichloromethane and the solution chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (52 mg).

MS (ESP): 467 (MH^+) for $C_{23}H_{23}FN_6O_4$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.83 (brs, 1.5H); 3.42 (t, 2H); 3.47 (brs, 1.5H); 3.77 (dd, 1H); 4.15 (t, 1H); 4.74 (m, 2H); 5.40 (brs, 1H); 7.26 (m, 2H); 7.44 (d, 1H); 7.71 (overlapping m, 3H); 8.02 (s overlapping m, 2H); 8.21 (brt, 1H); 8.50 (d, 1H).

Example 86: N-[(5S)-3-(3-Fluoro-4-(thiazol-2-ylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-thiocarbamidoimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (150 mg, 0.5 mM) was dissolved in DMF (2 ml), and stirred under nitrogen with bromoacetaldehyde diethylacetal (200 mg, 1 mM) at 110° for 2 hours. After dilution with 5% sodium bicarbonate solution (20 ml), the mixture was extracted with dichloromethane (2 x 10 ml), the extract washed with water and dried over magnesium sulfate. After evaporation the residue was dissolved in dichloromethane and the solution chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (41 mg).

MS (ESP): 402 (MH^+) for $C_{18}H_{16}FN_5O_3S$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.18 (t, 1H); 4.77 (m, 1H); 7.47 (dd, 1H); 7.63 (d, 1H); 7.77 (overlapping m, 2H); 7.82 (d, 1H); 8.08 (d, 1H); 8.13 (d, 1H); 8.22 (brt, 1H).

The intermediate N-[(5S)-3-(3-fluoro-4-(4-thiocarbamidoimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide was prepared as follows :-

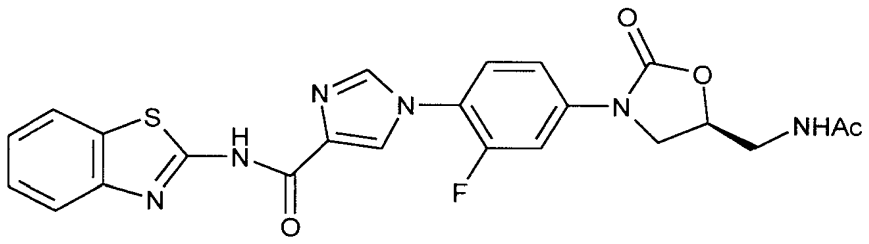
N-[(5S)-3-(3-Fluoro-4-(4-cyanoimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (WO97/31917; 686 mg, 2 mM) was dissolved in pyridine (30 ml), and triethylamine (1 ml, 7.2 mM) added. The mixture was stirred under a condenser cooled to -80°, and hydrogen sulfide gas introduced through a bubbler, until an excess was present, as judged by the appearance of liquid drops on the condenser. The mixture was stirred for 18 hours, the coolant in the condenser being allowed to evaporate. Excess hydrogen sulfide was removed under mild vacuum, and the solution diluted with diethyl ether (100 ml). The precipitate was

filtered, washed with a little diethyl ether, then dichloromethane, to give the desired product as a solid (800 mg).

MS (CI): 378 (MH^+) for $C_{16}H_{16}FN_5O_3S$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.42 (t, 2H); 3.78 (dd, 1H); 4.16 (t, 1H); 4.76 (m, 1H); 7.45 (dd, 1H); 7.74 (overlapping m, 2H); 8.07 (s, 1H); 8.11 (s, 1H); 8.22 (brt, 1H); 9.13 (brs, 1H); 9.48 (brs, 1H).

Example 87: N-[(5S)-3-(3-Fluoro-4-(2-benzothiazolylaminocarbonylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide



N-[(5S)-3-(3-Fluoro-4-(4-carboxyimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (1.81 g, 5 mM) and 1-hydroxybenzotriazole (0.81 g, 6 mM) were dissolved in DMF (40 ml) and stirred under nitrogen at ambient temperature. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide methiodide (1.78 g, 6 mM) was added, and the mixture stirred at ambient temperature for 2 hours, before adding 2-aminobenzothiazole (0.75 g, 5 mM). After stirring for 5 days, the mixture was diluted slowly with saturated aqueous sodium bicarbonate solution (20 ml), then water added to 250 ml. The fine precipitate was filtered, and recrystallised from a mixture of acetic acid (30 ml) and water (20 ml) to give title product (1 g).

MS (ESP): 495 (MH^+) for $C_{23}H_{19}FN_6O_4S$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.43 (t, 2H); 3.78 (dd, 1H); 4.14 (t, 1H); 4.77 (m, 1H); 7.31 (t, 1H); 7.31 (t, 1H); 7.49 (dd, 1H); 7.76 (overlapping m, 3H); 7.99 (d, 1H); 8.22 (brt, 1H); 8.24 (s, 1H); 8.51 (s, 1H); 11.98 (brs, 1H).

The compound shown in Example 60 is formed initially in this reaction, but rearranges to the product of Example 87 in the acidic conditions of the recrystallisation.

Example 88 :

The following illustrate representative pharmaceutical dosage forms containing a compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	179
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3
(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	229
	Croscarmellose sodium	12
	Polyvinylpyrrolidone	6
	Magnesium stearate	3
(c)	Tablet III	mg/tablet
	Compound X	1
	Lactose Ph.Eur	92
	Croscarmellose sodium	4
	Polyvinylpyrrolidone	2
	Magnesium stearate	1
(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	389
	Croscarmellose sodium	100
	Magnesium stearate	1
(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	Isotonic aqueous solution	to 100%

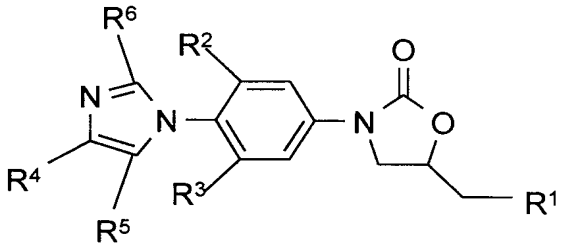
Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A compound of formula **(I)**,



(I)

wherein R^1 is hydroxy, amino, chloro, fluoro, (1-4C)alkanesulfonyloxy, azido, (1-4C)alkoxy, or of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

R^5 and R^6 are independently selected from hydrogen, (1-4C)alkyl, halo and trifluoromethyl;

R^4 is -X-Y-Het.;

wherein X is a direct bond or -CH(OH)- and

Y is $-(CH_2)_m-$, $-(CH_2)_n-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$ or $-C(=O)O-(CH_2)_m-$;

or wherein X is $-(CH_2)_n-$ or $-CH(Me)-(CH_2)_m-$ and

Y is $-(CH_2)_m-NH-(CH_2)_m-$, $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$, $-C(=S)NH-(CH_2)_m-$, $-C(=O)O-(CH_2)_m-$ or $-S(O)_p-(CH_2)_m-$;

or wherein X is $-CH_2O-$, $-CH_2NH-$ or $-CH_2N(R)-$ [wherein R is (1-4C)alkyl] and

Y is $-CO-(CH_2)_m-$, $-CONH-(CH_2)_m-$ or $-C(=S)NH-(CH_2)_m-$; and additionally Y is $-SO_2-$ when X is $-CH_2NH-$ or $-CH_2N(R)-$ [wherein R (1-4C)alkyl], and Y is $-(CH_2)_m-$ when X is $-CH_2O-$ or $-CH_2N(R)-$, and Y is additionally $-CON(R)-(CH_2)_m-$ [wherein R is (1-4C)alkyl], when X is a direct bond;

wherein n is 1, 2 or 3; m is 0, 1, 2 or 3 and p is 0, 1 or 2; and when Y is $-(CH_2)_m-NH-(CH_2)_m-$ each m is independently selected from 0, 1, 2 or 3;

wherein Het. is a heterocyclic ring [which heterocyclic ring may be unsaturated (linked via either a ring carbon or ring nitrogen atom to -X-Y-) or saturated (linked via a ring nitrogen atom to -X-Y-), with the proviso that when it is unsaturated and linked via nitrogen to -X-Y-

the ring is not quaternised] which heterocyclic ring is optionally substituted on an available carbon atom by up to three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkyl S(O)p- (wherein p is 0, 1 or 2), carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, amino, N-(1-4C)alkylamino, di(N-(1-4C)alkyl)amino or (1-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkyl S(O)p- (wherein p is 0, 1 or 2), carboxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, (2-4C)alkenyl, cyano, nitro, amino, imino, (2-4C)alkanoylamino, (1-4C)alkoxy, di(N-(1-4C)alkyl)aminomethylimino, hydroxy, oxo or thioxo (=S); and optionally substituted on an available nitrogen atom (if the ring will not thereby be quaternised) by (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkyl S(O)p- (wherein p is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di(N-(1-4C)alkyl)amino or (1-4C)alkanoylamino] or oxo (to form an N-oxide); and pharmaceutically acceptable salts thereof.

2. A compound of formula **(I)** as claimed in claim 1, wherein R^1 is acetamido; one of R^2 and R^3 is hydrogen and the other is fluoro; R^5 and R^6 are hydrogen; the -X-Y- link is $-CH_2S-$, $-CH_2O-CO-$, $-CH_2NH-$, $-CH_2NHCO-$ or -CONH-; the Het. moiety in R^4 is a fully unsaturated (aromatic) ring linked via a ring carbon atom and selected from furan, pyrrole, thiophene, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- and 1,2,4-triazole, 1,2,4- and 1,3,4-thiadiazole, oxazole, isoxazole, oxazine, thiazole and isothiazole, indole, quinoline, isoquinoline, benzpyrrole, benzpyrazole, benzimidazole, quinoxaline, benzthiazole, benzoxazole, benzthiadiazole, benztriazole and 1,4-benzodioxan; wherein the Het. moiety is optionally substituted by up to two substituents on an available carbon atom selected from (1-4C)alkyl, halo, cyano, nitro, amino, (2-4C)alkanoylamino, (1-4C)alkoxy, hydroxy, oxo and thioxo (=S), and optionally substituted by a substituent on an available nitrogen atom selected from (1-4C)alkyl and oxo; and pharmaceutically-acceptable salts thereof.

3. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in either of claims 1 and 2, wherein the Het. moiety is a monocyclic ring.

4. A compound of formula **(I)** as claimed in either of claims 1 and 2 selected from the group consisting of :-

N-[(5S)-3-(3-Fluoro-4-(4-pyrimidin-2-ylthiomethylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-furoyloxymethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyridin-2-ylaminomethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(quinoxalin-2-ylcarbonylaminomethyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(thiazol-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide; and pharmaceutically-acceptable salts thereof.

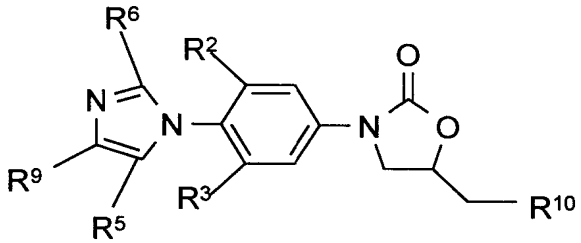
5. A compound of formula **(I)** as claimed in either of claims 1 and 2, selected from :-

N-[(5S)-3-(3-Fluoro-4-(4-(thiazol-2-ylaminocarbonyl)imidazol-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and

N-[(5S)-3-(3-Fluoro-4-(thiazol-2-ylimidazol-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide; and pharmaceutically-acceptable salts thereof.

6. A process for preparing a compound of formula **(I)**, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof (where R^1 to R^6 and other variables are as defined for formula **(I)** in claim 1) which comprises any of the following processes (a) to (i):-

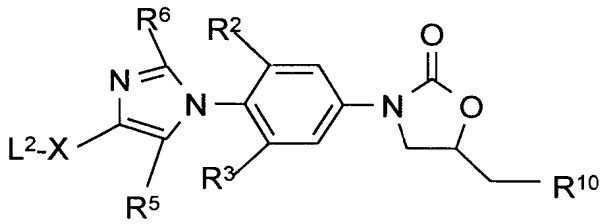
(a) by modifying a substituent in or introducing a substituent into another compound of the formula (I) or (II), or modifying a linking group in another compound of the formula (I) or (II);



(II)

wherein R^9 is R^4 or protected R^4 and R^{10} is R^1 or protected R^1;

(b) by reaction of a compound of the formula (III) with a compound of the formula Het-Y-L^1 [wherein L^1 and L^2 are independently hydrogen or a leaving group], or with a compound capable of forming a Het. moiety [wherein L^2 may form part of the final Het. moiety], or with a Het-Y-L^1 compound such that -Y-L^1 or L^2-X- (or a part thereof) may form part of the final -X-Y- link;

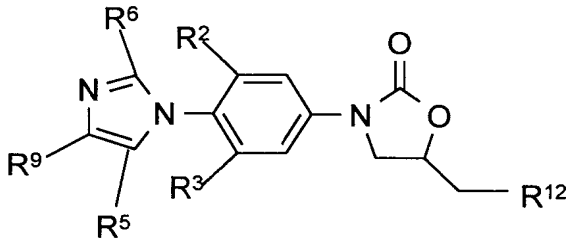


(III)

(c) when R^1 or R^{10} is of the formula -NHC(=O)R^a, by introducing -C(=O)R^a into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

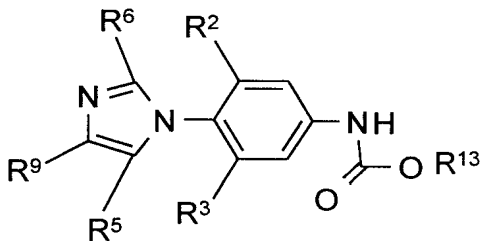
(d) when R^1 or R^{10} is amino, by reducing a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

(e) when R^1 or R^{10} is azido, by reacting a compound of the formula (IV) [wherein R^{12} is mesyloxy, tosyloxy or a phosphate ester] with a source of azide:

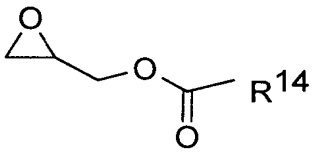


(IV)

(f) when R^1 or R^{10} is hydroxy, by reacting a compound of the formula (V) with a compound of the formula (VI) [wherein R^{13} is (1-6C)alkyl or benzyl, and R^{14} is (1-6C)alkyl]:



(V)



(VI)

(g) when R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl [wherein R^{15} is (1-4C)alkyl or benzyl], from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(h) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(i) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (IV); and thereafter if necessary i) forming a pharmaceutically acceptable salt, ii) forming an *in vivo* hydrolysable ester or iii) deprotecting; and when an optically active form of a compound of the formula **(I)** is required, it may be obtained by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure.

7. A pharmaceutical composition which comprises a compound of the formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, and a pharmaceutically acceptable diluent or carrier.

8. The use of a compound of the formula **(I)** of the present invention, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

9. A method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula **(I)** of the present invention, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/GB 98/03496

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/14 C07D417/14 A61K31/42 C07D413/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 31917 A (ZENECA LTD) 4 September 1997 see claims ---	1-9
Y	WO 96 23788 A (PHARMACIA & UPJOHN COMPANY) 8 August 1996 see claims ---	1-9
Y	EP 0 352 781 A (E.I DU PONT DE NEMOUR AND COMPANY) 31 January 1990 see claims ---	1-9
Y	WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see page 8, line 26 - page 9, line 26; claims ---	1-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 1999	03/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/03496

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 see claims	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03496

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. ational Application No
PCT/GB 98/03496

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9731917 A	04-09-1997	AU 1887697 A	16-09-1997
WO 9623788 A	08-08-1996	AU 4899896 A	21-08-1996
		BR 9607017 A	28-10-1997
		CA 2208603 A	08-08-1996
		CN 1172484 A	04-02-1998
		CZ 9702314 A	12-08-1998
		EP 0807112 A	19-11-1997
		FI 973217 A	04-08-1997
		JP 10513446 T	22-12-1998
		NO 973550 A	03-10-1997
		PL 321663 A	22-12-1997
EP 0352781 A	31-01-1990	US 4948801 A	14-08-1990
		AU 622465 B	09-04-1992
		AU 3911589 A	01-02-1990
		CA 1337526 A	07-11-1995
		DK 374389 A	30-01-1990
		FI 893618 A	30-01-1990
		JP 2124877 A	14-05-1990
		PT 91315 A	08-02-1990
		US 5130316 A	14-07-1992
		US 5043443 A	27-08-1991
		US 5254577 A	19-10-1993
WO 9309103 A	13-05-1993	AT 146783 T	15-01-1997
		AU 667198 B	14-03-1996
		AU 2689892 A	07-06-1993
		CA 2119556 A	13-05-1993
		DE 69216251 D	06-02-1997
		DE 69216251 T	15-05-1997
		DK 610265 T	09-06-1997
		EP 0610265 A	17-08-1994
		GR 3022340 T	30-04-1997
		JP 7500603 T	19-01-1995
		US 5565571 A	15-10-1996
		US 5801246 A	01-09-1998
		US 5654428 A	05-08-1997
		US 5756732 A	26-05-1998
		US 5654435 A	05-08-1997
WO 9507271 A	16-03-1995	AU 687866 B	05-03-1998
		AU 7557094 A	27-03-1995
		CA 2168560 A	16-03-1995
		CN 1130379 A	04-09-1996
		EP 0717738 A	26-06-1996
		JP 9502436 T	11-03-1997
		NZ 271805 A	26-02-1998
		ZA 9405894 A	05-02-1996